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(54) **Title:** PROCESS FOR PREPARING SACCHARINIC ACIDS AND LACTONES

(57) **Abstract:** An improved process for preparing a saccharinic acid or lactone is disclosed that utilizes the well-known Amadori rearrangement reaction. The synthesis utilizes protected or unprotected sugars or their analogues as starting materials, and reagents not previously utilized to afford increased product yields in decreased reaction time.

PROCESS FOR PREPARING SACCHARINIC ACIDS AND LACTONES

Cross-reference to Related Applications

This application claims the benefit of priority to U.S. Provisional Application No. 60/711,934, filed August 26, 2005, the disclosure of which is incorporated by reference.

Field of the Invention

This invention provides the synthesis of saccharinic lactones and acids for use as intermediates in syntheses of other compounds, most notably, herbicidal esters and branched nucleosides, the latter of which are useful in pharmaceutical compositions for the treatment of viral diseases and cancers as well as in the synthesis of vitamins B_{12} and L.

Background of the Invention

As progenitors of nucleotides and proteins, nucleosides, nucleoside analogues, their prodrugs and their intermediates offer a wide range of structural possibilities for the formation of new compounds that are useful in the treatment of diseases. A key area of interest is the synthesis of sugar analogues that can be used as intermediates in processes for preparing nucleosides.

Walton described KB cell-inhibitory branched-chain nucleosides prepared by reacting 2,3,5-tri-*O*-acyl-2-(or 3)-*C*-alkylribofuranosyl halides with chloromercuric purine or pyrimidine compounds (U.S. 3,480,613). 3-Lower alkyl-D-ribofuranosyl halide intermediates were prepared from 1,2-*O*-isopropylidene-5-*O*-acyl-α-D-erythro-pentofuran-3-ulose by reacting this compound with a Grignard reagent to add a lower alkyl group at C3; then subjecting the compound to acidic alcoholysis to form an alkyl 5-*O*-acyl-3-lower-alkyl D-ribofuranoside, acylating the latter to the alkyl 2,3,5-tri-*O*-acyl-3-lower alkyl-D-ribofuranoside, and converting the resulting ribofuranoside to a free sugar by subjecting it to a basic solvolysis and further hydrolysis in strong acid, or converting it to a halogenose by a halogen replacement reaction in appropriate

solvent. Alternatively, the 5-*O*-acyl-1,2-*O*-isopropylidene-3-lower alkyl-D-ribofuranose was acylated under basic conditions (pyridine) in inert solvent to form 3,5-di-*O*-acyl-1, 2-*O*-isopropylidene-3-lower alkyl-D-ribofuranose, then hydrolyzed in strong acid and further acylated to provide the desired intermediates. 2-substituted, 6-substituted or 2,6-disubstituted purine nucleosides having a branched-chain at the 2'- or 3'-position on the sugar moiety were then prepared by reacting 2,3,5-tri-*O*-acyl-D-ribofuranosyl halide with a chloromercuric 2,6-disubstituted purine at temperatures of 100°C to 140°C in a solvent such as toluene or xylene. Nucleosides having a pyrimidinone base were derived from a 2,3,5-tri-*O*-acyl-2 (or 3)-*C*-lower alkyl-D-ribofuranosyl halide by reaction with a 2,4-dialkoxy-pyrimidine to form 1-(2,3,5-tri-*O*-acyl-2 (or 3)-*C*-lower alkyl-D-ribofuranosyl)-4-alkoxy-2(1H)-pyrimidone, then reacted with ammonia or a primary or secondary amine to afford compounds having an amino substituent at the C-4 on pyrimidinone, or hydrolyzed under acidic or basic conditions to afford a pyrimidinone base having a hydroxy group at C-4. Unfortunately, Walton's syntheses involve multiple steps, special conditions, and numerous, toxic reagents.

Idenix Pharmaceuticals disclosed methods and compositions for treating hosts infected with hepatitis C, flaviviruses or pestiviruses comprising administration of certain 1', 2' or 3'-branched nucleosides (U.S. Patent Nos. 6,914,054 and 6,812,219; WO 01/90121; and WO 01/92282; see also U.S. 2004/0077587, WO 2004/003000 and WO 2004/002999).

Storer et al. disclosed an improved process for the synthesis of 2'-C-methyl nucleosides and 2'-C-methyl-3'-O-ester nucleosides in U.S. 2005/0020825 and WO 2004/003000. In one embodiment, the preparation of the 2'-C-methyl nucleosides utilized reacting D-fructose with calcium oxide to produce a 2-C-methyl lactone intermediate which was then processed further to prepare the desired branched nucleosides. Storer disclosed improved conditions which included the use of calcium oxide followed by treatment with CO_2 and oxalic acid that in some cases resulted in improved yields and reduced reaction times compared to the prior art process.

A process for the one-pot selective acylation of 2' or 3'-branched nucleosides to produce 3'-O-acyl branched nucleosides is disclosed in U.S. 2004/0181051 by Storer et al.

Bhat et al. disclosed certain branched nucleoside compounds which are useful as antiviral agents (U.S. Patent No. 6,777,395). The synthesis of the nucleoside

compounds was also disclosed. Branched nucleosides are also disclosed in U.S. 2004/0110717 and WO 04/000858 to Carroll et al., U.S. 2004/0067901, U.S. 2004/0072788 and WO 04/007512 to Bhat et al., WO 04/009020, WO 04/003138 to Olsen et al.

Stuyver et al. disclosed branched nucleosides in U.S. 2004/0002476 and U.S. 2003/0225029.

Interest in branched sugar compounds as synthetic intermediates is not limited to the area of nucleoside chemistry. S. Gogoi and N. Argade described a 6-step synthesis for preparing the ester (+)-*erythro* potassium 2,3,4-trihydroxy-2-methyl-butanoate, a leaf-closing substance isolated from the legume, *Leucaena leucocephalam* (Tetrahedron (2004) *60*:9093-9097). The synthetic route involved a branched sugar lactone diol intermediate. The leaf-closing substance operates in cooperation with another ester, potassium aeshynomate, a leaf-opening substance. Together, both esters respond to the plant's circadian rhythm, and account for the closing of its leaves in the evening and opening of its leaves in the morning. The agricultural uses of these esters as potential herbicides are currently being explored.

Sugar analogues:

Branched sugar compounds are available commercially. These compounds play a critical role in the syntheses of branched chain nucleosides. One important intermediate in certain of these processes is the formation of 2-*C*-methyl-D-ribonolactone. Scheibler described a synthesis for preparing this lactone by treating D-fructose with calcium hydroxide at temperatures of up to 100°C (John Sowden, *Adv. Carbohydrate Chem.*, 12:43-46 (1957), citing C. Scheibler, *Berichte* 13:2212 (1880)). Unfortunately, product yields were low at about 10% (Id.). In 1882, H. Kiliani synthesized 2-*C*-methyl-D-ribonolactone using the same reactants as Scheibler has used, but held reaction mixtures at room temperature for long periods rather than increasing reaction temperatures (H. Kiliani, *Berichte*, 15:2953 (1882), as cited in F.J. Lopez-Herrera et al., *J. Carbohydrate Chemistry*, 13(5):767-775 (1994)). Kiliani's process required months to run to completion and afforded no better product yields than Scheibler's process had done (Id. at 768). However, Kiliani's observations allowed him to establish the positions of several functional groups on the lactone (John Sowden, *Adv. Carbohydrate Chem.*, 12:43-46 (1957), citing H. Kiliani, *Ann.*, 213:361 (1883); Figure 2).

Whistler and BeMiller tried to improve upon the synthesis of Scheibler and Kiliani by repeatedly adding boiling water and calcium hydroxide to D-fructose, flushing the reaction with nitrogen gas, treating the mixture with carbon dioxide and oxalic acid dihydrate, filtering and washing until a syrup-like residue was obtained, evaporating the solvent and allowing the resultant product to crystallize (Roy L. Whistler and J.N. BeMiller, *Methods in Carbohydrate Chemistry*, 2:484-485 (1963)). The final product yield of 2-*C*-methyl-D-ribono-1,4-lactone was about 11% (Id. at 485).

As an alternative to the Scheibler and Kiliani synthesis, Lopez-Aparicio et al. reported the synthesis of 2-*C*-methyl-D-ribono-1,4-lactone from 2,3-*O*-isopropylidene-D-glyceraldehyde (Lopez-Aparicio et al., *Carbohydrate Res.*, 129:99 (1984), as cited in F.J. Lopez-Herrera et al., *J. Carbohydrate Chemistry*, 13(5):767-775 (1994) at 768-9). The Lopez-Aparicio synthesis included condensing 2,3-*O*-isopropylidene-D-glyceraldehyde with (1-methoxycarbony-ethylidene)triphenylphosphorane to produce methyl-E-(S)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-methyl-2-pentenoate; hydrolyzing in HCl and photochemically isomerizing the pentenoate; lactonizing the pentenoate product to produce a butenolide; tritylating the butenolide with trityl-chloride and pyridine; and treating the tritylated product with *cis*-hydroxylation with potassium permanganate and methylene chloride in the presence of a crown ether (Id.). Although Lopez-Aparicio et al. reported ribonolactone product yields of about 80%, this yield has not been reproduced given the gram mass amounts of materials provided in the experimental section of the publication. Additionally, the Lopez-Aparicio synthesis is far more complex than the Kiliani synthesis, requiring the use of toxic reagents like potassium permanganate and specialized irradiation equipment to attain photochemical isomerization, and a minimum of 60 hours reaction time (Id. at 768, 770-772).

Other significant synthetic attempts to produce 2'-*C*-branched nucleosides, analogues and prodrugs thereof, include the following:

a) Walton et al. converted 2-*C*-methyl-D-ribonolactone into its 2,3,5-tri-*O*-benzoyl derivative, reduced this derivative with bis(3-methyl-2-butyl)borane to provide an anomeric mixture of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribofuranose, treating the anomeric mixture with benzoyl chloride in pyridine, and chromatographically separating the final product, 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-(β)-D-ribofuranose (Walton

et al., *J. Am. Chem. Soc.* , 88(19):4524-5 (1966)). Later Walton et al. described the synthesis of 2'-*C*-methyl-5-fluorocytidine, 2'-*C*-methyl-5-fluorouridine, and 2'- and 3'-*C*-methyl-cytidine *via* the Hilbert-Johnson reaction (Walton et al., *Antiviral Nucleosides*, 12:306-9 (1969)). Unfortunately, large amounts of O-glycoside formed when 2'-*C*-methylcytidine was synthesized from N-acetylcytosine-mercury, itself a toxic reagent, and product yield was only about 11% (Id.).

b) Harry-O'Kuru described a synthesis for preparing 2'-*C*-branched ribonucleosides from commercially available 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose that was oxidized with Dess-Martin periodinane, stirred with excess $MgSO_4$, filtered, and treated with MeMgBr/$TiCl_4$ to produce an anomeric mix of desired 1,3,5-tri-*O*-benzoyl-2-substituted alkyl-, alkenyl-, or alkynyl-ribofuranosides and their transesterifed isomers, α- and β-2,3,5-tri-*O*-benzoyl-2-substituted alkyl, alkenyl or alkynyl ribofuranosides in a nearly 5:3 ratio (Harry-O'Kuru et al., *J. Org. Chem.*, 62:1754-9 (1997)). The alkylated ribofuranosides then were converted to a single, desired product, 1,2,3,5-tetrabenzoyl-2-alkylribofuranoside, by treatment with benzoyl chloride, DMAP and triethylamine in approximately a 70% yield with a β/α ratio of 4:1 (Id.).

c) Novak and Sorm reported the synthesis of crystalline 2-*C*-methyl-D-ribose from 2-*C*-methyl-D-ribonolactone *via* a sodium borohydride reduction (Novak & Sorm, *Collection Czechoslov. Chem. Comm.*, 34:857-866 (1969)). Their work provided a comparison of reactivities of the hydroxy group on the lactone, which was easily acetylated under conditions known to those of skill in the art to 2,3,5-tri-*O*-acetyl- and 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribonolactone, with the similarly situated hydroxy group on the ribofuranoside, for which the same reaction conditions produced only 3,5-di-*O*-acetyl- and 3,5-di-*O*-benzoyl-2-*C*-methyl-D-ribofuranosides (Id.).

d) Novak later disclosed chiral-optical properties of 2-methyl-1,4-lactones that were prepared from D-xylose and D-lyxose *via* a hypoiodite oxidation reaction and that had *p*-toluoyl protecting groups at C3 and C5 on the lactone (Novak, *Collection Czechoslov. Chem. Comm.*, 39:869-

882 (1974)). However, Novak described difficulty in separating the protected lactone products from one another (Id. at 871).

e) Beigelman et al. described the synthesis of 2'-*C*-methyl-nucleosides from D-glucose and D-ribose (Beigelman et al., *Carbohydrate Res.*, 166:219-232 (1987)). Using D-glucose as a starting material, 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose was prepared and converted by selective incorporation of a *p*-methylbenzoyl group *via* formation of a 5,6-*O*-dibutylstannylidene derivative, followed by treatment with trifluoroacetic acid, periodate oxidation, elimination of the formyl group and acetylation (Id.). Alternatively, using D-ribose as a starting material, a 2,3-dimethyl-isopropylidene derivative having a protected 5-position was subjected to aldol condensation with formaldehyde, and then treated with excess toluene-*p*-sulfonyl chloride in pyridine (Id.). In both cases, percent product yield was about 75-80%, but required costly materials and reagents (Id.).

f) Both Tokyo Tanabe Co., Ltd., (JP 61-212592) and BASF Aktiengesellschaft (EP 0 288,847) reported epimerization processes for preparing unprotected D-ribose from D-arabinose. Although their processes differ, both epimerizations require sophisticated and expensive equipment and reagents, and provide a product that still requires the addition of protective groups.

g) Japan Tobacco, Inc., prepared 3-DPA-lactone by protecting the 5-OH group on a γ-ribonolactone, reacting the latter with an acid chloride or an acid anhydride that has a tertiary amine in order to cause β-elimination of the 3-OH group with formation of a double bond between carbons 2 and 3 and simultaneous acylation of the 2-OH, catalytically hydrogenating the double bond between C2 and C3, and finally removing the protective group and regenerating the 5-OH (EP 0 526,655 A1; EP 0 553,358 A1; and EP 0553,358 B1; and their U.S. equivalents, US 5,322,955 and US 5,391,769).

Related work on syntheses of ribonolactones and sugar analogues with protected substituents include:

i) Li et al., *Organic Letters,* **3(7)**:1025-28 (2001) synthesized 2'-*C*-β-trifluoromethyl pyrimidine ribonucleoside from 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose,

and then converted it to 3,5-di-*O*-benzoyl-2-*C*-β-trifluoromethyl-α-D-1-ribofuranosyl bromide. The latter bromide derivative compound was found to be an effective reaction intermediate in the formation of nucleosides;

ii) Beigelman et al., *Bioorg. Khim.*, **12(10)**:1359-65 (1986), synthesized 2-C-methyl-D-ribose derivative compounds *via* benzylation of 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose to form a first intermediate; hydrolyzed and selectively acylated the first intermediate to form 3-*O*-benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-6-*O*-toluoyl-α-D-allofuranose; and sequentially deisopropylidenated, oxidized (with periodic acid), deformylated, acetylated, debenzylated and acetylated again to provide 1,2,3-tri-*O*-acetyl-2-*C*-methyl-5-*O*-toluoyl-β-D-ribofuranose as a final product;

iii) Feast et al., *Acta Chemica Scandinavica* **19**:1127-34 (1965), reported the preparation of α-D-glucosaccharinic acid, shown to be 2-*C*-methyl-D-ribo-pentonic acid, by alkaline treatment of D-fructose or 1-*O*-substituted D-fructose *via* a 1,4-lactone intermediate;

iv) Kohn et al., *J.Am.Chem.Soc.*, **87(23):**5475-80 (1965), described a short route for obtaining a furanose derivative of an aldose, by reducing a tetraacylhexono-γ-lactone to its corresponding tetraacylhexofuranose through use of disiamylborane as a reducing agent. The reaction is particularly important for the formation of intermediates in the synthesis of C-1' furanosyl nucleosides;

v) Kempe et al., *Nucleic Acids Res.,* **10(21**):6695-6714 (1982) reported the selective 2'-benzoylation at the *cis* 2',3'-diols of protected ribonucleosides and isomerization of 2'-benzoates to 3'-benzoates. These protected nucleosides were used to synthesize oligoribonucleotides on solid silica gel supports; and

vi) U.S. 4,294,766 in which Schmidt et al. detailed the synthesis of pure ribonolactone as an intermediate in the formation of riboflavin (vitamin B_2) from a mixture of ribonolactone and arabonolactone. A mixture of potassium arabonate and potassium ribonate was "lactonized" by methods known in the art (such as by using H_2SO_4 or K_2SO_4 and filtering off the precipitate), and the resulting lactone mixture, of which about 70% was ribonolactone, was separated by fractional crystallization using dioxane or ethylene glycol monomethyl ether.

It is therefore an object of the invention to provide an improved process for preparing a saccharinic lactones and acids which may be used as intermediates in the synthesis of nucleosides.

It is another object of the present invention to have an efficient process for preparing a branched sugar analogue compound that involves a minimal number of steps, runs to completion in a matter of hours, and utilizes an inexpensive starting material.

It is another object of this invention to have a process that employs easily handleable, non-toxic reagents, and whose final product is easily isolated by techniques commonly known in the art.

It is another object of the present invention to provide a process that is readily scaleable for industrial manufacture.

Summary of the Invention

The present invention discloses a synthetic method for the preparation of saccharinic lactones and acids via an Amadori rearrangement reaction that comprises the treatment of an amino-substituted sugar molecule with a base, and then optionally with an acid. To our knowledge, the use of the Amadori rearrangement reaction to provide amino-substituted sugars that can then be utilized to produce a saccharinic lactone has not been previously disclosed.

The process of the present invention utilizes the Amadori reaction for the synthesis of a saccharinic lactone from an aldose by reaction of the aldose with a secondary amine to form a 1-amino-1-deoxy ketose, and subsequent treatment of that ketose with a base. The process also involves the treatment of an unprotected sugar with an amine, and a subsequent step of treating the water soluble secondary amine with a strong base without a purification step. The synthetic method is advantageous in that it utilizes inexpensive sugars as starting materials, thereby providing significant cost savings. This is especially important where scale-up for industrial applications is required or envisioned. In addition, the process can provide an improvement in the yield, in some cases, an increase of 8% or more is possible.

In a general embodiment, a process for preparing a saccharinic acid or lactone is provided that includes a) reacting a sugar compound with a disubstituted amine to

provide a corresponding disubstituted amino sugar; b) reacting the disubstituted amino sugar with a base and optionally subsequently with an acid to afford a saccharinic acid or lactone product; c) optionally reacting the saccharinic acid or lactone product with a protecting group; and d) optionally isolating and purifying the saccharinic acid or lactone product. A saccharinic lactone in various stereoisomeric and tautomeric forms may be achieved.

In one embodiment, the process includes the preparation of a saccharinic lactone via an Amadori rearrangement reaction. In certain subembodiments, the process includes utilizing D-glucose as a starting material in a 2-step synthesis to prepare 2-*C*-methyl-D-ribono-1,4-lactone. In yet another embodiment, the present invention utilizes other sugar molecules as starting materials in the same Amadori rearrangement reaction to prepare a desired lactone or acid.

Brief Description of the Drawings

Figure 1 is a generalized schematic of the Amadori rearrangement reaction and subsequent base treatment of the Amadori rearrangement product.

Figure 2 is a schematic of the novel process for preparing 2-*C*-methyl-D-ribono-lactone from D-glucose.

Figure 2a is a schematic of an alternative novel process for for preparing 2-*C*-methyl-D-ribono-lactone from D-glucose.

Figure 3 is a schematic of the process of the present invention for preparing 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C*-methyl-D-xylono-1,4-lactone from 1-deoxy-1-(*N,N*-dibenzylamino)-D-tagatose.

Figure 4 is a schematic of the novel process for preparing 2-*C*-methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone from 1-deoxy-1-(*N,N*-dibenzylamino)-D-tagatose.

Figure 5 depicts the process of the present invention for preparing 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone from D-galactose.

Figure 6 is a schematic of the novel process of the present invention for preparing 2-*C*-methyl-D-threono-1,4-lactone and 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone from D-xylose.

Figure 7 illustrates the process of the present invention for preparing 2-*C*-methyl-D-threono-1,4-lactone from D-xylose.

Figure 7a illustrates the process of the present invention for preparing 2-*C*-methyl-D-threono-1,4-lactone and 2-*C*-methyl-D-erythrono-1,4-lactone from D-xylose.

Figure 8 depicts the process of the present invention for preparing 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone from 2-*C*-methyl-D-threono-1,4-lactone.

Figure 9 is a schematic of the novel process for preparing 2-*C*-methyl-L-erythrono-1,4-lactone and 2-*C*-methyl-L-threono-1,4-lactone from L-arabinose.

Figure 10 illustrates a schematic of the novel process for preparing 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone from 2-*C*-methyl-L-threono-1,4-lactone.

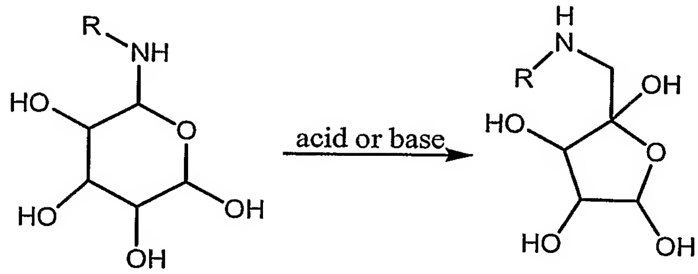
Figure 11 depicts the process of the present invention for preparing 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone from 2-*C*-methyl-L-erythrono-1,4-lactone.

Figure 12 depicts a prior art synthesis of a branched-sugar nucleoside that utilizes a ribonolactone intermediate (U.S. Application Serial No. 10/735,408 (pending)).

Detailed Description of the Invention

The process of the present invention utilizes a known rearrangement reaction, the Amadori reaction, for the synthesis of a saccharinic acid or lactone from an unprotected aldose by reacting the aldose with an amine to form a 1-amino-1-deoxy-ketose, and subsequently directly treating the 1-amino-1-deoxy-ketose first with a base without an intermediate purification step, and then optionally with an acid. The synthetic method is advantageous in that it utilizes inexpensive sugars as starting materials, thereby providing significant cost savings.

The Amadori rearrangement reaction first was elucidated by M. Amadori as a means of preparing a 5-membered methylamino sugar from a 6-membered amino sugar by treatment with an acid or base, as illustrated in the following scheme (*Atti. Accad. Nazl. Lincei*, 2(6):337 (1925):



It is now known that the Amadori reaction is not limited to a 6-membered sugar as a starting material, and that any size sugar ring may be used.

The concept underlying the present invention is that an Amadori rearrangement product that is reacted with a base, such as calcium oxide, to form a saccharinic acid or lactone could provide an alternative to the base mediated reaction of fructose which proceeds *via* a methyldiketone intermediate to produce the same saccharinic acid or lactone. It has been discovered that the alteration of the "leaving group" at carbon C-1 of fructose could improve the yield of saccharinic lactone product.

Reaction times and yields vary with the particular sugar and amine used for the Amadori reaction. For example, dibenzylamine rendered the Amadori products insoluble in water, and necessitated a longer reaction time, occasionally up to three days, when reacted with calcium oxide and afforded a lower yield of lactone product. Sugars other than glucose or fructose can be used in the same synthetic process with good product yields. Surprisingly, the use of dimethylamine consistently resulted in a water soluble product, and the use of calcium oxide as a base afforded a reaction time of approximately 24 hours that was independent of the sugar used.

The synthetic method of the present invention in provides a reasonable yield of the lactone products, including about 35% product yield in some circumstances. This is an improvement over the prior art work of both Kiliani and of Whistler and BeMiller, and facilitates industrial scalability. Kiliani's synthesis provided a product yield of about 11% 2-*C*-methyl-D-ribono-1,4-lactone from the treatment of inverted sucrose with calcium hydroxide at room temperature over about a 6-10 week period (H. Kiliani, *Berichte*, 15:2953 (1882). Whistler and BeMiller also attained approximately an 11% 2-*C*-methyl-D-ribono-1,4-lactone product yield from either D-fructose or inverted sucrose (a mixture of D-glucose and D-fructose) (Roy L. Whistler

and J.N. BeMiller, *Methods in Carbohydrate Chemistry*, 2:484-485 (1963)). Their reaction utilized calcium hydroxide as a base and proceeded at room temperature for about 8 weeks (Id.). In one example of the present invention, an approximately 19% product yield of 2-*C*-methyl-D-ribono-1,4-lactone was obtained from D-glucose over about a 24 hour period when the reaction with acid was omitted in the second step of the process.

Principal Embodiments

In a first embodiment, the process of the present invention is directed to the preparation of 2-*C*-methyl-D-ribono-1,4-lactone by reacting D-glucose with a disubstituted amine (aliphatic, i.e. alkyl, alkeny or alkynyl or alkaryl, i.e. benzyl) to provide 1-deoxy-1-(*N,N*-disubstituted amino)-D-fructose, which is then reacted with a base and a strong protic acid to afford 2-*C*-methyl-D-ribono-1,4-lactone. In one subembodiment, dimethylamine may be used to provide 1-deoxy-1-(*N,N*-dimethylamino)-D-fructose, which is then reacted with calcium oxide and sulfuric acid to afford 2-*C*-methyl-D-ribono-1,4-lactone. In another subembodiment, dibenzylamine may be used. In one subembodiment, sulfuric acid may be used. In one embodiment, the present invention utilizes unprotected D-glucose as the starting material in an Amadori rearrangement reaction with dibenzylamine to provide 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose, which is then reacted with calcium oxide and sulfuric acid to afford 2-*C*-methyl-D-ribono-1,4-lactone.

In a subembodiment of the first embodiment, the starting material D-glucose is suspended in ethanol/glacial acetic acid and, after reaction with dimethylamine to afford a crude oil product, is dissolved in water before the addition of base and acid.

In another subembodiment of the first embodiment, anhydrous D-glucose is suspended in ethanol, and then reacted with dibenzylamine in glacial acetic acid prior to the addition of a base and acid.

In yet another subembodiment of the embodiment, reaction of a secondary amine with a base is enhanced by first charging the base, then heating the resulting amine/charged base mixture for a sufficient amount of time. In one non-limiting example, the mixture is heated for about 20 hours, and finally stirring the mixture for about an additional 3 to 5 hours before the addition of an acid.

In a second embodiment, the process is directed to the preparation of 2-*C*-methyl-D-ribono-1,4-lactone by reacting a D-glucose with a disubstituted amine

dimethylamine and then a base. In one subembodiment, D-glucose is reacted with dimethylamine and then with calcium hydroxide as a base.

In another subembodiment of the second embodiment, 2-*C*-methyl-D-ribono-1,4-lactone was prepared by reacting D-glucose with dimethylamine and then with calcium oxide as the base, followed by the addition of an acid.

In a third embodiment, the present invention was used to prepare 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C*-methyl-D-xylono-1,4-lactone as products from the reaction of D-galactose with a disubstituted amine, and then subsequently with a base and optionally with an acid. In one non-limiting example, the amine is dibenzylamine and the base is calcium oxide.

In a subembodiment of the third embodiment, the 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C*-methyl-D-xylono-1,4-lactone products were synthesized by the reaction of D-galactose with dimethylamine, a base, and optionally with an acid.

In a fourth embodiment, the present invention comprises reacting D-xylose with dimethylamine, and then with calcium oxide to provide 2-*C*-methyl-D-threono-1,4-lactone as a major product and 2-C-methyl-D-erythrono-1,4-lactone as a minor product.

In a subembodiment of the fourth embodiment, D-xylose was reacted with dimethylamine, and then with calcium oxide and acetone to provide 2-*C*-methyl-D-threono-1,4-lactone and 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone.

In yet a fifth embodiment, D-galactose was reacted with a disubstituted amine and then sequentially with a base and acetone to afford 3,5-*O*-isopropylidene 2-*C*-methyl-D-xylono-1,4-lactone as a product. In a subembodiment, the amine is dimethylamine and the base is calcium oxide.

A sixth embodiment comprises reacting L-arabinose with a disubstituted amine and then with a base to afford 2-*C*-methyl-L-threono-1,4-lactone and 2-*C*-methyl-L-erythrono-1,4-lactone. In a subembodiment, the amine is dimethylamine and the base is calcium oxide.

Subembodiments of all embodiments include the use calcium hydroxide in place of calcium oxide. Also, any appropriate amine of choice may replace dimethylamine or dibenzylamine as an Amadori reagent. Suggested alternative amines are provided below.

In one embodiment, the process includes suspending an aldose starting material in a solvent, adding a secondary amine, and reacting the mixture. The

resulting solution is then suspended with a base, neutralized and filtered to provide a 2-*C*-methyl-aldonolactone product. In certain embodiments, the reaction of the aldose and amine is carried out at from about 40°C to about 120°C for from about 10 minutes to about 10 hours. The reaction can form a dark orange-brown solution. In a subembodiment the reaction of the aldose and the amine is carried out from about 40°C to about 100°C. In another subembodiment, the reaction is carried out from about 60°C to about 80°C. In a further subembodiment, the reaction is carried out from about 70°C to about 90°C. In certain embodiments, the solution can be concentrated *in vacuo* to form a crude oil which can be dissolved in water. The solution or oil can them be stirred with the addition of a strong base. In one embodiment, the solution is stirred with the base at from about 20°C to about 120°C for from about 12 hours to about 96 hours to afford a suspension. In one subembodiment, the solution is stirred with a base at from about 40°C to about 100°C. In another subembodiment, the solution is stirred with the base at from about 50°C to about 90°C. In a further subembodiment, the solution is stirred from about 60°C to about 80°C. The suspension can be neutralized using an acid that is added to neutralize the suspension, and a precipitate is formed. In certain embodiments, the mixture is cooled to room temperature and filtered to provide the desired product compound, a 2-*C*-methyl-aldonolactone product.

In another embodiment, the process includes suspending an aldose starting material in a solvent, adding a secondary amine, and reacting the mixture at from about 40°C to about 120°C for from about 10 minutes to about 10 hours, then cooling the mixture to from about 30°C to about 90°C and maintaining the reaction mixture at this temperature for from about 1 to about 5 hours to form an orange-brown solution. In a subembodiment the reaction of the aldose and the amine is carried out from about 40°C to about 100°C. In another subembodiment, the reaction is carried out from about 60°C to about 80°C. In a further subembodiment, the reaction is carried out from about 70°C to about 90°C. In one subembodiment, the mixture is cooled to from about 30°C to about 60°C. In another subembodiment, the mixture is cooled to from about 25°C to about 50°C. The solution prepared according to this method can be concentrated *in vacuo* to form a crude oil, which is then dissolved in water before being stirred with the addition of a strong base added in aliquots at from about 10°C to about 75°C for from about 30 minutes to about 3 hours to afford a mixture. In certain embodiments, the mixture can be heated at from about 15°C to about 100°C for about

15 hours to about 35 hours, and then cooled to from about 0°C to about 25°C. In certain subembodiments, the mixture is heated at from about 30°C to about 80°C. In another subembodiment, the mixture is heated at from about 50°C to about 80°C. In another subembodiment, the mixture is heated at from about 60°C to about 80°C. In certain embodiments, an acid is added to the mixture over from about a 30 minute to about a 10 hour time period at a temperature of from about 0°C to about 25°C until an acidic pH (pH<7) is attained. The acidic mixture then can be heated to from about 25°C to about 100°C and stirred while maintaining the same temperature for from about 5 hours to about 25 hours. In this embodiment, the mixture is cooled to from about 0° to about 50°C and a precipitate is formed. The 2-*C*-methyl-aldonolactone product can be derived from the mixture. In certain embodiments, the mixture can be filtered, the filtrate concentrated, and acetone, water and Fuller's earth added. To enhance recovery, the concentrate can be heated to reflux for from about 5 minutes to about 3 hours, and, in certain embodiments, the upper liquid phase repeatedly decanted, collected and evaporated to provide a crude brown solid product, which is suspended in acetone. This suspended mixture can be cooled to from about 0°C to about 50°C, and stirred for from about 30 minutes to about 10 hours, filtered, and dried to provide the final product compound, a 2-*C*-methyl-aldonolactone product.

In yet another embodiment, the process comprises reacting an aldose starting material in a solvent, adding a secondary amine, and reacting the mixture at from about 40°C to about 120°C for from about 10 minutes to about 10 hours to form an orange solution. In a subembodiment the reaction of the aldose and the amine is carried out from about 40°C to about 100°C. In another subembodiment, the reaction is carried out from about 60°C to about 80°C. In a further subembodiment, the reaction is carried out from about 70°C to about 90°C. The solution then is cooled to from about 5°C to about 50°C, and stirred with the addition of a strong base at from about 20°C to about 120°C for from about 10 hours to about 96 hours. Next the mixture is cooled to from about 5°C. to about 50°C, filtered, and the filtrate passed through an acidic resin to provide a major product and a minor product. The products can be purified to afford two distinct diastereomeric 2-*C*-methyl-aldonolactone products.

In still another embodiment, a 1-amino-1-deoxy-ketose is reacted with a strong base to form a crude alkaline mixture and the purified to provide 2-*C*-methyl-aldonolactone products. The reaction can be carried out for from about 12 hours to

about 96 hours. The alkaline mixture can be cooled to room temperature and filtered prior to purification. The filtrate can be passed through an acidic resin and purified by procedures known to those skilled in the art to provide 2-*C*-methyl-aldonolactone products.

Yet another embodiment includes reacting a 1-amino-1-deoxy-ketose with a strong base, neutralizing the solution with an acid to afford a precipitate, and purifying the product to afford a 2-*C*-methyl-aldonolactone. In one embodiment, the reaction is carried out for from about 12 hours to about 96 hours. In certain embodiments, the precipitate is cooled and filtered through an acidic resin to provide a crude oil. The crude oil can be purified and dissolved in a solvent with the addition of standard protecting groups known to those skilled in the art. The protecting groups can be removed, along with the solvent, and the resulting product purified to afford a 2-*C*-methyl-aldonolactone.

Other non-limiting embodiments of the present invention comprise:

a) reacting an aldose with a secondary amine at from about 40 °C to about 120 °C for from about 10 minutes to about 10 hours to provide a crude oil product; reacting the crude oil product with a strong base at from about 20 °C to about 120 °C for from about 12 to about 96 hours to afford an unprotected 2-*C*-methyl-xylono-lactone product; and reacting the unprotected 2-C-methyl-xylono-lactone product with a protecting group known by those skilled in the art to afford a protected 2-*C*-methyl-xylono-lactone as a final product;

b) reacting an aldose with a secondary amine at from about 40 °C to about 120 °C for from about 10 minutes to about 10 hours, cooling the mixture to room temperature to produce a crude oil, reacting the crude oil with a strong base for from about 12 to about 96 hours, vigorously stirring the oil/base mixture with an acid, and purifying the product to afford 2-*C*-methyl-threono-lactone as one product; then reacting the purified oil/base mixture with acetone and an acid to afford 2,3-*O*-isopropylidene-2-*C*-methyl-erythrono-lactone as a second product;

c) reacting an aldose with a secondary amine from about 40 °C. to about 120 °C for from about 10 minutes to about 10 hours to

provide a crude oil, reacting the crude oil with a strong base at from about 20 °C to about 120°C for from about 12 to about 96 hours, cooling, filtering and purifying the resulting oil product to provide 2-*C*-methyl-threono-lactone as a final product; and

d) reacting an aldose with a secondary amine for from about 10 minutes to about 10 hours at from about 40°C to about 120°C to afford a crude oil, reacting the crude oil with a strong base, cooling the reaction mixture to provide a precipitate, filtering the precipitate through an acidic resin to provide 2-*C*-methyl-threono-lactone as a major product and 2-*C*-methyl-erythrono-lactone as a minor product.

e) reacting a suspension of D-glucose in glacial acetic acid and ethanol with a dimethylamine solution at about 20°C for about 30 minutes; heating the suspension in step (a) to about 75°C for about 30 minutes, then cooling and maintaining the suspension at about 55°C for about 3 hours to provide an orange solution; concentrating the orange solution *in vacuo* at about 50° to afford a brown oil; adding calcium oxide in aliquots to the brown oil to provide a mixture; evacuating the mixture under nitrogen gas flow; heating the mixture to about 25°C to about 40°C over about 18 hours to about 20 hours; stirring the mixture at about 40°C for about 4 hours, and then cooling the mixture to about 3°C; adding sulfuric acid to the mixture over about a 2 hour period to provide a yellow-colored mixture of pH at from about 2.4 to about 2.7; heating the mixture to about 45°C with stirring for about 12 hours, then cooling the mixture to about 25°C to precipitate calcium sulfate; filtering the calcium sulfate precipitate to provide a brown filtrate; reacting the brown filtrate with acetone and Fuller's earth in water to afford a mixture; refluxing the mixture and extracting with acetone to provide an upper and a lower liquid phase; and collecting, filtering and drying the upper liquid phase to provide 2-*C*-methyl-D-ribono-1,4-lactone.

f) A process for preparing 2-*C*-methyl-D-ribono-1,4-lactone from D-glucose comprising: reacting a suspension of D-glucose in glacial

acetic acid and ethanol with a dimethylamine or dibenzylamine solution at about 80°C for about 1.5 hours to provide a crude product mixture; dissolving the crude product mixture in water to afford an aqueous mixture; stirring the aqueous mixture with calcium oxide at about 70°C for about 24 hours to afford a suspension; adding oxalic acid dihydrate to the suspension; cooling the suspension to room temperature; filtering the suspension with water; isolating the filtrate to provide a crude lactone product; dissolving the crude product in water to afford a solution and heating the solution to about 40°C for about 15 minutes to provide an impure lactone product; and purifying the impure lactone product by chromatography to provide 2-*C*-methyl-D-ribono-1,4-lactone.

g) A process for preparing 2-*C*-methyl-D-ribono-1,4-lactone from D-glucose via 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose comprising: reacting a suspension of anhydrous D-glucose in absolute ethanol with dibenzylamine in glacial acetic acid solution; heating the dibenzylamine/glacial acetic acid solution to reflux for about 3 hours to provide a crude product mixture; cooling the crude product mixture to afford a precipitate; filtering the precipitate with ethanol to provide 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose as a solid; reacting the 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose solid with calcium oxide at about 70 °C. for about 48 hours to afford a suspension; adding oxalic acid dihydrate to the suspension; cooling the suspension to room temperature; filtering the suspension with water and isolating the filtrate to provide a crude lactone product; purifying the crude lactone product to afford a soluble product; and recrystallizing the soluble product to provide 2-*C*-methyl-D-ribono-1,4-lactone.

h) A process for preparing 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C*-methyl-D-xylono-1,4-lactone from D-galactose comprising: reacting a suspension of anhydrous D-galactose in absolute ethanol with dibenzylamine and glacial acetic acid solution at about 80 °C for about 2 hours to provide a crude product mixture; dissolving

the crude product mixture in water to afford a suspended precipitate; filtering the suspended precipitate to provide 1-deoxy-1-(*N,N*-dibenzyl amino)-α-D-tagatopyranose as a crystalline solid; reacting the 1-deoxy-1-(*N,N*-dibenzylamino)-α-D-tagatopyranose crystalline solid with calcium oxide at about 70 °C for about 24 hours to afford a mixture; cooling the mixture to room temperature; filtering the mixture with water to afford a crude oil; and purifying the crude oil to provide 2-*C*-methyl-D-lyxono-1,4-lactone as a major product and 2-*C*-methyl-D-xylono-1,4-lactone as a minor product.

i) In any one of the embodiments described the product may be purified by flash chromatography.

j) In one sub-embodiment, the sugar compound is D-xylose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-D-threono-1,4-lactone and 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone.

k) In another sub-embodiment the sugar compound is D-xylose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-D-threono-1,4-lactone and 2-*C*-methyl-D-erythrono-1,4-lactone.

l) In a further sub-embodiment the sugar compound is D-galactose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone product is 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone.

m) In another sub-embodiment the sugar compound is D-galactose, the disubstituted amine is dibenzylamine, the base is calcium hydroxide, and the saccharinic lactone product is 2-*C*-methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone.

n) In another sub-embodiment, the sugar compound is L-arabinose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-L-threono-1,4-lactone and 2-*C*- methyl-L-erythrono-1,4-lactone.

o) In another embodiment, a process for preparing an hydroxy-protected saccharinic lactone product is presented comprising, reacting the saccharinic lactone product with pyridine to afford a saccharinic lactone product solution; reacting the saccharinic lactone product solution with an hydroxy- protective reagent to form an hydroxy-protected saccharinic lactone product; and isolating and/or purifying the hydroxy-protected saccharinic lactone product.

p) In one subembodiment, the hydroxyl-protective reagent is acetic anhydride.

q) In one sub-embodiment, the saccharinic lactone product is 2-*C*-methyl-D-threono-1,4-lactone and the hydroxy-protected saccharinic lactone product is 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone.

r) In another sub-embodiment, the saccharinic lactone product is 2-*C*-methyl-L-threono-1,4-lactone and the hydroxy-protected saccharinic lactone product is 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone.

s) In another sub-embodiment, saccharinic lactone product is 2-*C*-methyl-D-lyxono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 2,3,5-tri-*O*-acetyl-2-*C*-methyl-D-lyxono-1,4-lactone.

t) In another embodiment, a process for preparing an hydroxy-protected saccharinic lactone product is presented comprising, reacting a saccharinic lactone product with an acidic solution to afford saccharinic lactone product solution; reacting the saccharinic lactone acidic product solution with an hydroxyl-protecting reagent to provide an hydroxyl-protected saccharinic lactone product; and isolating and/or purifying the hydroxy-protected saccharinic lactone product.

u) In one sub-embodiment of t) the acidic solution comprises acetone in a dilute *p*-toluenesulfuric acid solution.

v) In another sub-embodiment, the saccharinic lactone product is 2-*C*-methyl-D-xylono-1,4-lactone and the hydroxyl-protected

saccharinic lactone product is 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone.

w) In another sub-embodiment, the saccharinic lactone product is 2-*C*-methyl-D-erythrono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone.

x) In another sub-embodiment, the saccharinic lactone product is 2-*C*-methyl-L-erythrono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone.

Any of the lactone products prepared may be reacted with appropriate reagents to provide protected groups on the products, as known by those skilled in the art or as taught by Greene and Wuts, <u>Protective Groups in Organic Synthesis (John Wiley & Sons, Inc., 3rd Ed., New York, NY; 1999)</u>. Examples include a) reacting 1-deoxy-1-(N,N-dibenzylamino)-D-tagatose with calcium hydroxide, and then with *N,N*-dimethylaminopyridine and acetic anhydride to provide 2-*C*-methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone; b) reacting 2-*C*-methyl-D-threono-1,4-lactone in pyridine with DMAP and acetic anhydride at room temperature for about 3 hours, removing solvents, and purifying 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone as the resulting product; c) reacting 2-*C*-methyl-L-threono-1,4-lactone in pyridine with DMAP and acetic anhydride at room temperature for about 3 hours, removing solvents, and purifying the resulting product, 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone; and d) reacting 2-*C*-methyl-L-erythrono-1,4-lactone in *p*-toluenesulfonic acid with acetone at room temperature for about 14 hours, neutralizing the mixture with sodium carbonate to provide a residue, extracting, filtering and purifying the residue to afford 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone as a protected product.

For all embodiments, reaction progress can be monitored by electrospray ionization mass spectrometric (negative ion) analysis of crude samples at regular intervals. For example, disappearance of a peak at approximately 358 Daltons (Da) and appearance of a new peak at 179 Da indicated the completion of the reaction for the starting material and production of the desired anionic carboxylate product. Closure of the branched carboxylic acid to the saccharinic lactone was indicated by disappearance of the peak at 179 Da and the appearance of a new peak at 161 Da.

Repetitive observations of the disappearance and appearance of these peaks allows achievement of optimal reaction times and synthetic method scale-up.

Alternative Reactants and Reagents

The present invention is not limited to the specific reactants and reagents given for each step in the process but includes other, alternatives that are functional equivalents to those provided. For example, any amine amenable to the Amadori rearrangement may be used in this invention, including but not limited to primary amines and primary amine derivatives that can be functionalized by acylation, including alkyl and aryl primary amines; natural and non-natural amino acids; secondary amines, including N-alkyl amines, N-aryl amines, dialkyl amines, alkylidene-amines, aralkylamines, N-containing heterocycles such as morpholine, piperidine, pyrrolidine, N-methylaniline; and quaternary salts of Amadori ketoses.

Acid catalysts in addition to glacial acetic acid that may be used include, but are not limited to, weak acids such as pyridinium *p*-toluenesulfonate, carboxylic acids, quaternary ammonium acid, and secondary amine salts such as, for example, dimethylammonium acetate and dimethylammonium chloride.

Various sugars may be used as starting materials. Aldoses in particular are favored, including but not limited to D-glucose, D-galactose, D-xylose, L-arabinose, D-ribose, and glucuronic acid. Pentoses and heptoses also may be used, such as glucoheptose and mannonic acids.

Any possible proton acceptor and/or source of hydroxide ion in aqueous solution may serve as a base in the present invention. While calcium oxide is favored, any metal hydroxide or metal oxide may be used including but not limited to calcium hydroxide, barium hydroxide, strontium hydroxide, sodium hydroxide, potassium hydroxide, or any basic resin or any combination thereof.

Protection of isolated products that are synthesized by the inventive process include but are not limited to reactions that form acetals, ketals, esters, ethers, and oxygen-protecting groups like acetyl that provide protected or functionalized derivatives, but do not interfere with reactions that comprise the invention . Other reactions include, but are not limited to, any that afford a substituted or unsubstituted silyl, alkyl, aryl, or acyl group including any substituted or unsubstituted aromatic or aliphatic acyl, such as, for example, an aromatic acyl group like benzoyl, *p*-toluoyl, *p*-nitrobenzoyl, *p*-chlorobenzoyl; any ether group such as, for example, C-*O*-aralkyl, C-

O-alkyl, or C-*O*-aryl; and any aliphatic group like an acyl or acetyl group, where the alkyl is straight-chained or branched. All of which may be further optionally substituted by groups not affected by the reducing agent of choice, typically Red-Al (see Greene and Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, 3rd Edition (1999)).

The acidification step following treatment of the Amadori compound with base may be accomplished by any acid. For example, oxalic acid, Amberlite® IR 120 resin, sulfuric acid, any carboxylic acid, mineral acid, acid resin or any combinations of these may be used.

Isolation and purification techniques include but are not limited to chromatography and crystallization, and include any techniques known to those of skill in the art. Crystallizations may be performed by using one or more suitable solvents, including mixtures or neat samples of acetone, ethyl acetate, hexane, cyclohexane, ether, petrol, acetone, toluene, and the like, or by heating and cooling. Chromatography may embrace any chromatographic techniques including flash chromatography, utilizing solvents, and stationary phases as deemed appropriate. Useful solvents include but are not limited to mixtures or neat samples of acetone, ethyl acetate, hexane, cyclohexane, ether, petrol, acetone, toluene, and any known to those of skill in the art.

Definitions

The terms "saccharinic acid" and "saccharinic lactone" as used herein mean 2-*C*-methyl-aldonic acid and 2-*C*-methyl-aldonolactone respectively, and correspond to the historical definitions provided by Sowden (see John C. Sowden, "The Saccharinic Acids" in Advances in Carbohydrate Chemistry, 12:35-79 (1957) at 36-37, Melville L. Wolfromm and R. Stuart Tipson, Eds., Academic Press, Inc., New York).

In the present invention, the terms "ribonic-γ-lactone" and "ribonolactone" may be used interchangeably throughout.

The hydroxyl moieties on ribofuranose may have any of a variety of protecting groups including benzoyl; substituted or unsubstituted silyl groups; substituted or unsubstituted aromatic or aliphatic esters, such as, for example, aromatic groups like benzoyl, toluoyls, nitrobenzoyl, chlorobenzoyl; and groups like acyls, where an acyl is straight-chained or branched; all of which may be further optionally substituted by

groups not affected by the reactions comprising the improved synthesis (see Greene and Wuts, Protective Groups in Organic Synthesis, John Wiley and Sons, 3rd Edition (1999)).

The term "alkyl", as used herein and unless specified otherwise, includes to a saturated, straight, branched, or cyclic, primary, secondary or tertiary hydrocarbon of typically C_1 to C_{10}, and specifically includes methyl, trifluoromethyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *t*-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, methylpentyl and dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Moieties with which the alkyl group can be substituted in one or more positions are selected from the group consisting of halo (including fluorine, chlorine, bromine or iodine), hydroxyl (e.g. CH_2OH), amino (eg., CH_2NH_2, CH_2NHCH_3 or $CH_2N(CH_3)_2$), alkylamino, arylamino, alkoxy, aryloxy, nitro, azido (eg., CH_2N_3), cyano (CH_2CN), sulfonic acid, sulfate, phosphonic acid, phosphate or phosphonate, any or all of which may be unprotected or further protected as necessary, as known to those skilled in the art and as taught, for example, in Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, 2nd Edition (1991).

Whenever a range of carbon atoms is referred to, it includes independently and separately every member of the range. As a non-limiting example, the term "C_1-C_{10} alkyl" is considered to include, independently, each member of the group, such that, for example, C_1-C_{10} alkyl includes straight, branched and where appropriate cyclic C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10} alkyl functionalities.

The terms "alkylamino" and "arylamino" includes an amino group that has one or more alkyl or aryl substituents, respectively.

The terms "alkaryl" and "alkylaryl" include an alkyl group with an aryl substituent. The terms "aralkyl" and "arylalkyl" refer to an aryl group with an alkyl substituent.

The term "halo" includes chloro, bromo, iodo, and fluoro.

The term "aryl", as used herein, and unless specified otherwise, includes phenyl, biphenyl or naphthyl. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more moieties including but not limited to hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, any or all of which may be unprotected or further protected as necessary, as known to those skilled in the

art and as taught, for example, in Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, 2nd Edition (1991).

The term "acyl" includes a group of the formula C(O)R, in which R is for example, straight, branched, or cyclic alkyl or lower alkyl, amino acid, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, alkaryl, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono-, di- or tri-phosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl such as, for example, dimethyl-*t*-butylsilyl), or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

The terms "carboxylic acid" and "carboxylic acid ester" include groups of the formulas -C(O)OH and -C(O)OR, respectively. Where the non-carbonyl moiety, R, is for example, straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, alkaryl. Also intending for inclusion here are sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono-, di- or tri-phosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl such as, for example, dimethyl-*t*-butylsilyl), or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. In all occurrences, R and R' may be the same or may be different substituents.

The term amino acid includes naturally occurring and synthetic α, β, γ, or δ amino acids, and includes but is not limited to, amino acids found in proteins, *i.e.* glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration, but can also be used in the D-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleuccinyl, β-prolinyl, β-phenylalaninyl, β-

tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl.

The term "non-natural amino acid" refers to a carboxylic acid having an amino group terminus that is not found in nature. The term is intended to embrace both D- and L-amino acids, and any tautomeric or stereoisomeric forms thereof.

The term "protected", as used herein and unless specified otherwise, refers to a group that is added to a reactive group, including an oxygen, nitrogen or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen, nitrogen and phosphorus protecting groups are known to those skilled in the art of organic synthesis. For example, BOC (butoxycarbonyl) is one non-limiting protecting group, as are a variety of ethers, esters, acyl, and acetyl groups.

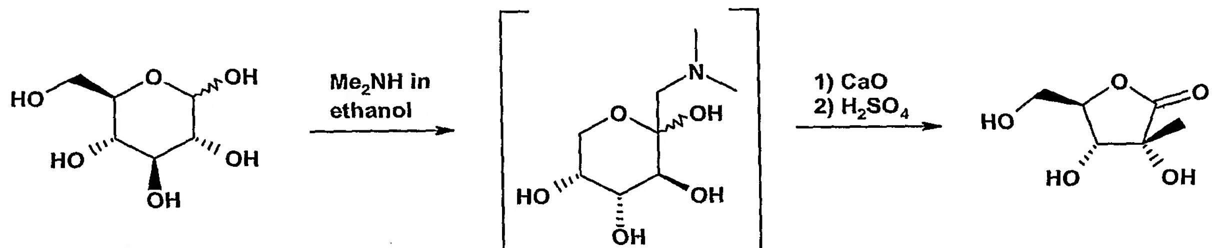
The abbreviation "TLC" as used herein refers to thin-layer chromatography, while "LRMS" as used here refers to mass spectrometry. The abbreviation "DMAP" refers to the base catalyst reagent, 4-dimethylaminopyridine, and the abbreviation "PTSA" means *para*-toluenesulfuric acid.

Throughout this application, the term "substituted" includes single or multiple degrees of substitution by one or more named substituents. Where a single substituent is disclosed or claimed, the compound can be substituted once or more than once by that substituent. Where multiple substituents are disclosed or claimed, the substituted compound can be substituted independently by one or more of the disclosed or claimed substituent moieties, singly or plurally.

This invention is further illustrated in the following non-limiting examples. The working examples contained herein are set forth to aid in understanding the invention. They are illustrative of the process(es) and product(s) of the invention, but are not intended to and should not be interpreted to in any way limit the invention set forth in the claims that follow thereafter. Equivalent, similar or suitable starting materials, solvents, reagents, or reaction conditions may be substituted for those particular starting materials, solvents, reagents, and/or reaction conditions described herein without departing from the spirit and scope of the invention.

Examples

Example 1. Synthesis of 2-*C*-Methyl-D-ribono-1,4-lactone from D-Glucose



D-glucose

1-deoxy-1-(*N*,*N*-dimethylamino-D-fructose

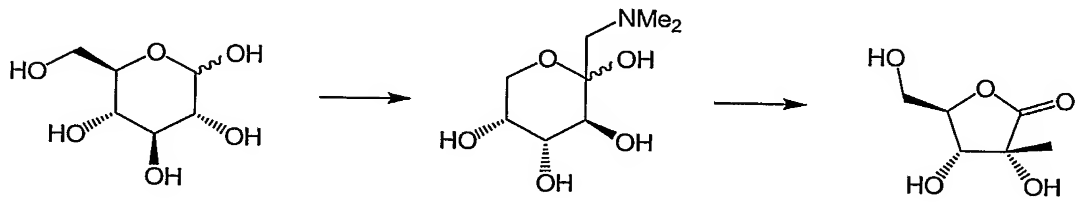
Compound 2

2-C-methyl-D-ribono-1,4-lactone

D-Glucose (90.1 g) was suspended in absolute ethanol (130 mL) with acetic acid (30.0 g) and was charged to a reactor at 20 °C. Dimethylamine solution (33% solution in absolute ethanol, 69.7 g) was added to the suspension within 30 minutes at 20 °C (exothermic), and a dropping funnel employed for additions to the reactor was rinsed with absolute ethanol (5 mL). The reaction mixture was heated to 75 °C. within a 30 minute period, then cooled to 55 °C. within 1 hour, and maintained at 55 °C. for an additional 2 hours, to afford a orange solution. The orange solution then was concentrated at 50 °C. *in vacuo* to provide a brown oil. Water (190 g) was then added to the brown oil, and the reactor was evacuated three times to approximately 100 mbar and each time was relieved with nitrogen, following which a weak nitrogen flow was continued. Calcium oxide (36.5 g) was added in 4 portions at 10 minute intervals at 15 °C., with rises of approximately 5 °C. in internal temperature observed after addition of each portion. The reactor was evacuated twice to approximately 100 mbar and relieved with nitrogen, following which a weak nitrogen flow was continued. The mixture then was heated to an internal temperature of 25 °C within about 20 minutes, then heated to an internal temperature of 40 °C. within 18 hours, following which it was stirred at an internal temperature of 40 °C for four hours, and finally cooled to an internal temperature of 3 °C. 96% sulfuric acid (80.6 g) was added over a 2 hour period while maintaining an internal temperature of 3 °C to provide a yellow colored mixture. The pH was checked to reach a targeted pH of between 2.4 and 2.7;

if the pH was >2.7, sulfuric acid was added to reach the target value. The yellow mixture next was heated to an internal temperature of 45 °C within 30 minutes, stirred for 12 hours while maintaining the 45 °C internal temperature, and then cooled to 25 °C. Calcium sulfate that formed was removed by filtration through a scintered glass funnel into a 2 L. filter flask, and the filtration residue was washed via the reactor in three portions of water (100 g per portion) to provide a brown filtrate. This filtrate was concentrated at a temperature of 50 °C and pressure of 40 mbar by use of a rotary film evaporator, and then was degassed at 50 °C and 20 → 10 mbar for 1 hour. Next, acetone (500 mL), water (50 g) and Fuller's earth (50 g) were added to the concentrated filtrate, and this mixture was refluxed for 30 minutes, after which the upper liquid phase was decanted and filtered through a cellflock pad. The lower phase was extracted twice with acetone (250 mL) and water (25 g) under reflux for 5 minutes. The upper liquid phase was decanted and filtered through a cellflock pad for each of the two extractions. Next, the combined filtrates were concentrated at a temperature of 50 °C and 450 mbar by using a rotary film evaporator, and the degassed at 50 °C and 20 → 10 mbar for 1 hour to provide 60.8 g of crude product as a dark brown solid. Acetone (90 mL) was added to the crude product at a temperature of 60 °C. over a 10 minute time period, and the mixture was stirred at 60 °C., then at an internal temperature of 50-56 °C for 5-15 minutes to afford a suspension in a volume of 200 mL. Next, the mixture containing the suspension was cooled to an internal temperature of 20 °C, and the contents were stirred for 2 hours while maintaining the internal temperature at 20 °C. The mixture then was filtered through a scintered glass funnel (porosity 3), and the filter cake washed twice with acetone (15 mL) at room temperature to provide the final product. The final product was dried in vacuum at 50 °C for 5 hours to afford 28.7 g of 2-*C*-Methyl-D-ribono-1,4-lactone as a yellow-white solid.

Example 2. **Synthesis of 2-*C*-Methyl-D-ribono-1,4-lactone from D-Glucose**

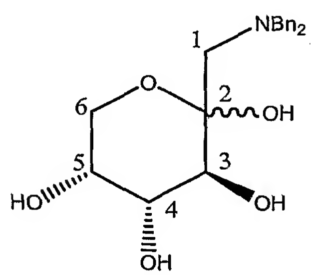


D-glucose — 1-deoxy-1-(*N*,*N*-dimethylamino)-D-fructose — 2-*C*-methyl-D-ribono-1,4-lactone

D-Glucose (3.17 g, 17.6 mmol) was suspended in ethanol (5 mL) with glacial acetic acid (1 mL). Dimethylamine solution (33% solution in methylated spirits, 3.2 mL, 18.0 mmol) was added to the suspension and the reaction mixture stirred at 80 °C for one and a half hours. The resulting dark orange solution was concentrated *in vacuo* to afford a crude dark orange-brown oil (6.55 g). The crude product mixture was then dissolved in water (150 mL) and stirred at 70 °C with calcium oxide (5.61 g, 100 mmol) for 24 hours when TLC analysis (chloroform:methanol:water:acetic acid, 60:30:5:3) revealed no starting materials (R_f 0.09 & 0.24) and only baseline products. LRMS analysis (ESI -ve) of the crude alkaline reaction mixture showed only one major peak at 179.01 Da. Oxalic acid dihydrate (6.74 g, 53.5 mmol) was added to the suspension to afford a pale pink precipitate suspended in a solution with a measured pH of 10. The mixture was allowed to cool to room temperature, filtered through a pad of Celite® with water and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. The water was then removed under reduced pressure to afford a crude orange oil (2.39 g). The crude product was dissolved in water (50 mL) and heated at 40 °C for 15 minutes. TLC analysis (15% methanol in dichloromethane) revealed the presence of one major product (R_f 0.38) and LRMS analysis (ESI –ve) revealed no peak at 179.01 Da and a major peak at 161.15 Da. The water was removed under reduced pressure and the crude product purified by flash column chromatography (ethyl acetate:cyclohexane, (1:1) → ethyl acetate) and subsequently by recrystallisation from ethyl acetate by the addition of cyclohexane to afford 2-*C*-methyl-D-ribono-1,4-lactone (534 mg, 19%) as a white crystalline solid; mp 158-159 °C {Lit. 160-161 °C}; $[\alpha]_D^{13.5}$ +87.5 (c 0.76 in water) {Lit. $[\alpha]_D^{20}$ +93 (water)}; ν_{max}(film): 3356 (br, O-H), 1773 (γ-lactone C=O) cm^{-1}; δ_H (CD_3OD, 400

MHz): 1.40 (3H, C$\underline{H}_3$), 3.71 (1H, dd, $J_{4,5}$ 4.5 Hz, $J_{5,5'}$ 12.8Hz, H-5), 3.90 (1H, d, $J_{3,4}$ 7.8 Hz, H-3), 3.94 (1H, dd, $J_{4,5'}$ 2.4 Hz, $J_{5,5'}$ 12.8 Hz, H-5'), 4.29 (1H, ddd, $J_{4,5}$ 4.5 Hz, $J_{4,5'}$ 2.4 Hz, $J_{3,4}$ 7.8 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 20.02 ($\underline{C}H_3$), 60.03 (C-5), 72.55 (C-2), 72.64 (C-3), 83.43 (C-4), 176.97 (C-1); LRMS m/z (ESI -ve): 161.04 (M-H^+, 100%), 183.00 (M+Na^+-2H^+, 47%); HRMS m/z (ESI -ve): found 161.0455 (M-H^+); $C_6H_9O_5$ requires 161.0450.

<u>Example 3.</u> Preparation of 1-Deoxy-1-(*N,N*-dibenzylamino)-D-fructose

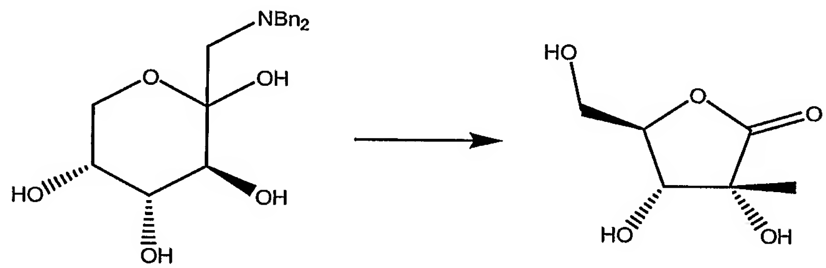


$C_{20}H_{25}NO_5$
Exact Mass: 359.17
Mol. Wt.: 359.42
C, 66.83; H, 7.01; N, 3.90; O, 22.26

Anhydrous D-glucose (3.62 g, 20.1 mmol) was suspended in absolute ethanol (20 mL). Dibenzylamine (3.85 mL, 20.1 mmol) and glacial acetic acid (1.14 mL, 19.9 mmol) were added and the suspension heated under reflux for three hours with continuous stirring. Solution of the D-glucose occurred after an hour and a half to yield a yellow solution. Crystallisation of the product in the reaction flask occurred shortly afterwards. The cooled mixture was filtered with suction and the filter cake washed with ethanol until the ethanolic washings were colourless. The filter cake was then dried *in vacuo* to afford 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose (6.24 g, 86%) as a white crystalline solid; mp 163-164 °C {Lit. 165-166 °C}; $[\alpha]_D^{15}$ -40.6 (*c* 1.7 in 1.0M $HCl_{(aq)}$) {Lit. $[\alpha]_D^{25}$ -40 (*c* 1.0 in pyridine)}; ν_{max} (film): 3286 (O-H) cm^{-1}; δ_H (($CDCl_3$, 400 MHz): 2.46 (1H, s, 5-OH), 2.54 (1H, s, 4-OH), 2.74 (1H, d, C$\underline{H}_2$NBn$_2$), 3.04 (1H, d, C$\underline{H}_2$NBn$_2$), 3.36 (1H, d, H-3), 3.47 (2H, d, NC$\underline{H}_2$(C_6H_5)$_2$), 3.60 (1H, m, 3-OH), 3.73 (2H, m, H-4 & H-5), 3.97 (2H, d, H-6 & H-6'), 4.01 (1H, s, 2-OH), 4.10 (2H, d, NC$\underline{H}_2$(C_6H_5)$_2$), 7.25-7.37 (10H, m, NCH_2($C_6\underline{H}_5$)$_2$); δ_C (d^5-pyridine, 100.6 MHz): 59.90 (C-1), 60.27 (2xN$\underline{C}H_2$Ph), 65.66 (C-6), 71.98 (C-5), 72.64 (C-4), 73.02 (C-3), 100.73 (C-2), 128.66, 129.97, 130.91, 140.72 (C_6H_5); LRMS m/z (ESI +ve): 360.33 (M+H^+, 100%); HRMS m/z (ESI +ve): found 360.1809 (M+H^+); $C_{20}H_{26}NO_5$

requires 360.1811. Found: C, 66.79; H, 7.00; N, 3.89; $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.90.

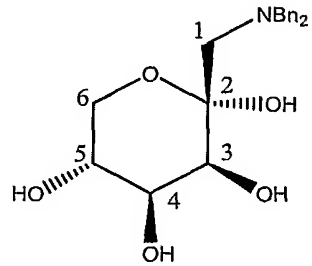
Example 4. Synthesis of 2-*C*-Methyl-D-ribono-1,4-lactone from 1-Deoxy-1-(*N,N*-dibenzylamino)-D-fructose



1-Deoxy-1-(*N,N*-dibenzylamino)-D-fructose (10.83 g, 30.18 mmol) was suspended in water (150 mL) and stirred at 70 °C with an aqueous suspension of calcium oxide (1.0 M, 200 mL) for 48 hours when TLC analysis (15% methanol in dichloromethane) revealed no starting material (R_f 0.63) and only baseline products which were not fluorescent under UV light. LRMS analysis (ESI -ve) of the crude alkaline reaction mixture showed only one major peak at 179.03 Da. Oxalic acid dihydrate (16.73 g, 132.7 mmol) was added to the suspension to afford a white precipitate suspended in a solution with a measured pH of 0. The mixture was allowed to cool to room temperature, filtered and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. The water was then removed under reduced pressure to afford a crude orange oil (6.74 g). TLC analysis (15% methanol in dichloromethane) revealed the presence of one major product (R_f 0.38) which was purified by flash column chromatography (ethyl acetate) and subsequently by recrystallisation from ethyl acetate by the addition of cyclohexane to afford 2-*C*-methyl-D-ribono-1,4-lactone (625 mg, 13%) as a pale beige crystalline solid; mp 158-159 °C {Lit. 160-161 °C}; $[\alpha]_D^{13.5}$ +87.5 (*c* 0.76 in water) {Lit. $[\alpha]_D^{20}$ +93 (water)}; ν_{max} (film): 3356 (br, O-H), 1773 (γ-lactone C=O) cm^{-1}; δ_H ((CD_3OD, 400 MHz): 1.40 (3H, s, C$\underline{H}_3$), 3.71 (1H, dd, $J_{4,5}$ 4.5 Hz, $J_{5,5'}$ 12.8Hz, H-5), 3.90 (1H, d, $J_{3,4}$ 7.8 Hz, H-3), 3.94 (1H, dd, $J_{4,5'}$ 2.4 Hz, $J_{5,5'}$ 12.8 Hz, H-5'), 4.29 (1H, ddd, $J_{4,5}$ 4.5 Hz, $J_{4,5'}$ 2.4 Hz, $J_{3,4}$ 7.8 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 20.02 ($\underline{C}H_3$), 60.03 (C-5), 72.55 (C-2), 72.64 (C-3), 83.43 (C-4), 176.97 (C-1); LRMS m/z (ESI -ve): 161.04

($M-H^+$, 100%), 183.00 ($M+Na^+-2H^+$, 47%); HRMS m/z (ESI -ve): found 161.0455 ($M-H^+$); $C_6H_9O_5$ requires 161.0450.

Example 5. 1-Deoxy-1-(*N*,*N*-dibenzylamino)-α-D-tagatopyranose from D-Galactose

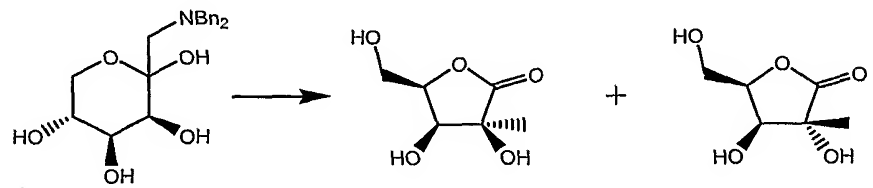


$C_{20}H_{25}NO_5$
Exact Mass: 359.17
Mol. Wt.: 359.42
C, 66.83; H, 7.01; N, 3.90; O, 22.26

Anhydrous D-galactose (14.26 g, 79.2 mmol) was suspended in absolute ethanol (80 mL). Dibenzylamine (15.5 mL, 80.9 mmol) and glacial acetic acid (4.5 mL, 78.6 mmol) were added and the suspension stirred at room temperature for 20 minutes and then heated at 80 °C for two hours with continuous stirring. The reaction mixture was concentrated under reduced pressure and water (100 mL) was added to afford a dark brown solution. Slow addition of this solution to water (100 mL) afforded a suspended precipitate. The suspension was filtered with suction and the filter cake washed with methanol (2 x 50 mL). The filter cake was then washed once more with water and then dried *in vacuo* to afford 1-deoxy-1-(*N*,*N*-dibenzylamino)-α-D-tagatopyranose (25.10 g, 88%) as a pale yellow crystalline solid. Samples of the crystals were recrystallised from a water/dioxane mixture and from hot methanol for X-ray analysis; mp 124-125 °C {Lit. 128-131 °C}; $[\alpha]_D^{21}$ +10.4 (*c* 1.2 in CH_3OH) {Lit. $[\alpha]_D^{21}$ +60 (*c* 1.0 in pyridine)}; ν_{max} (film): 3333 (O-H), 2850 (C-H) cm^{-1}; δ_H ((CD_3OD, 400 MHz): 2.72 (1H, d, $J_{1,1'}$ 13.7 Hz, H-1), 2.86 (1H, d, $J_{1,1'}$ 13.7 Hz, H-1'), 3.43 (1H, d, $J_{3,4}$ 3.1 Hz, H-3), 3.57-3.74 (5H, m, H-4, H-6, H-6' & $NC\underline{H}_2Ph$), 3.76-3.86 (3H, m, H-5 & $NC\underline{H}_2Ph$), 7.22-7.41 (10H, m, $NCH_2(C_6\underline{H}_5)_2$); δ_C (CD_3OD, 100.6 MHz): 58.96 (C-1), 59.10 ($2xN\underline{C}H_2Ph$), 62.94 (C-6), 67.09 (C-5), 72.23 (C-4), 74.59 (C-3), 96.67 (C-2), 127.34, 128.48, 129.40, 138.75 (C_6H_5); LRMS m/z (ESI +ve): 360.33 ($M+H^+$, 100%); HRMS m/z (ESI +ve): found 360.1812 ($M+H^+$); $C_{20}H_{26}NO_5$ requires

360.1811. Found: C, 66.59; H, 7.05; N, 3.89; $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.90.

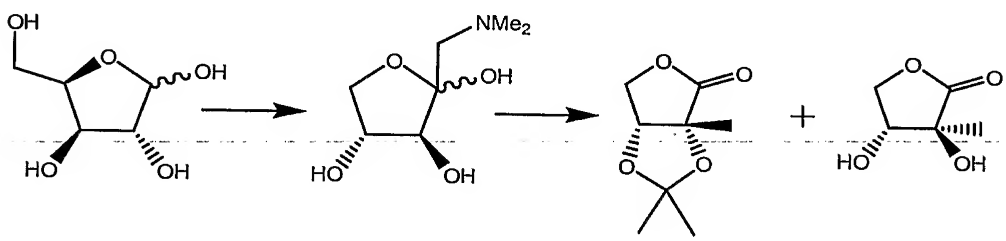
Example 6. Synthesis of 2-*C*-Methyl-D-lyxono-1,4-lactone & 2-*C*-Methyl-D-xylono-1,4-lactone



1-Deoxy-1-(*N,N*-dibenzylamino)-D-tagatose (3.04 g, 8.47 mmol) was suspended in water (100 mL) and stirred at 70 °C with calcium oxide (4.24 g, 75.7 mmol) for 24 hours when TLC analysis (ethyl acetate) revealed only baseline products. LRMS analysis (ESI -ve) of the crude alkaline reaction mixture showed only one major peak at 179 Da. The mixture was allowed to cool to room temperature, filtered through Celite® and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. The water was then removed under reduced pressure to afford a crude orange oil (724 mg). TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.16) and two minor products (R_f 0.27 & 0.32). Purification by flash column chromatography (ethyl acetate) afforded 2-*C*-methyl-D-lyxono-1,4-lactone (166 mg, 12%, R_f 0.16) as a colourless oil and 2-*C*-methyl-D-xylono-1,4-lactone (26 mg, 2%, R_f 0.32) as a white crystalline solid which was recrystallised from an ethyl acetate/methanol mixture by addition of cyclohexane. *Data for 2-C-methyl-D-lyxono-1,4-lactone*: $[\alpha]_D^{23}$ +70.4 (*c* 0.9 in $(CH_3)_2CO$) {Lit. for 2-*C*-methyl-L-lyxono-1,4-lactone $[\alpha]_D^{19}$ -79 (*c* 4.0 in water)}; ν_{max} (film): 3421 (O-H), 1773 (γ-lactone C=O), 1638 (water) {Lit. ν_{max}: 1778 (lactone), 1630 (water)} cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.43 (3H, s, C<u>H</u>$_3$), 3.88 (2H, d, $J_{4,5}$ 5.5 Hz, 2 x H-5), 4.07 (1H, d, $J_{3,4}$ 3.8 Hz, H-3), 4.54 (1H, dt, $J_{4,5}$ 5.5 Hz, $J_{3,4}$ 3.8 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 20.66 (<u>C</u>H$_3$), 60.42 (C-5), 74.18 (C-3), 74.54 (C-2), 81.50 (C-4), 179.34 (C-1); LRMS m/z (ESI -ve): 161.07 (M-H^+, 74%), 251.19 (M+CH_3OH+$(CH_3)_2CO$-H^+, 100%); HRMS m/z (ESI -ve): found 161.0449 (M-H^+); $C_6H_9O_5$ requires 161.0450. *Data for 2-C-methyl-D-xylono-1,4-lactone*: mp 161-162 °C {Lit. for 2-*C*-methyl-L-xylono-1,4-

lactone mp 159-162 °C}; $[\alpha]_D^{23}$ +87.3 (*c* 0.5 in water) {Lit. $[\alpha]_D^{20}$ +93.1 (*c* 0.8 in water)}; ν_{max} (film): 3254 (O-H), 1776 (γ-lactone C=O) {Lit. ν_{max}: 1775 (lactone)} cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.39 (3H, s, $C\underline{H}_3$), 3.82-3.90 (2H, m, H-5 & H-5'), 4.03 (1H, d, $J_{3,4}$ 3.7 Hz, H-3), 4.71 (1H, ddd, $J_{3,4}$ 3.7 Hz, $J_{4,5}$ 5.0 Hz, $J_{4,5'}$ 6.4 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 16.80 ($\underline{C}H_3$), 60.38 (C-5), 75.33 (C-3), 76.49 (C-2), 82.85 (C-4), 178.17 (C-1); LRMS m/z (ESI -ve): 161.11 ($M-H^+$, 100%); HRMS m/z (ESI -ve): found 161.0452 ($M-H^+$); $C_6H_9O_5$ requires 161.0450. Found: C, 44.37; H, 6.21; $C_6H_{10}O_5$ requires C, 44.45; H, 6.22.

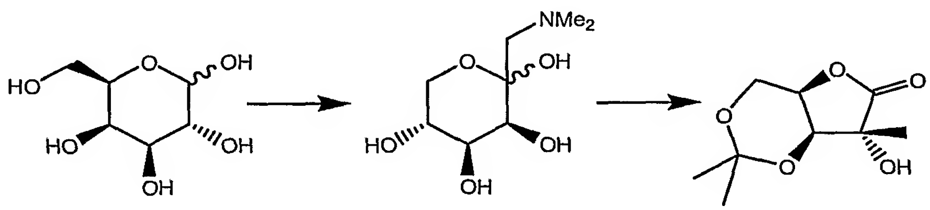
Example 7. **Synthesis of 2-*C*-methyl-D-threono-1,4-lactone & 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone from D-Xylose**



D-Xylose (9.72 g, 64.8 mmol) was suspended in ethanol (15 mL) with glacial acetic acid (3.8 mL). Dimethylamine solution (33% solution in methylated spirits, 12.3 mL, 69.2 mmol) was added to the suspension and the reaction mixture stirred at 80 °C for 40 minutes and then allowed to cool to room temperature over an hour. The resulting dark orange solution was concentrated *in vacuo* to afford a crude dark red oil. LRMS analysis (ESI -ve) revealed a major peak at 176.14 Da. The crude product mixture was dissolved in water (300 mL) and stirred at 70 °C with calcium oxide (12.95 g, 231 mmol) for 24 hours. Dilute sulfuric acid (2M) was carefully added with vigorous stirring until the measured pH of the solution was 7. The mixture was allowed to cool to room temperature, filtered through a pad of Celite® with water and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. TLC analysis (ethyl acetate) revealed the presence of two major products (R_f 0.44 & R_f 0.56). The water was removed under reduced pressure to afford a crude dark brown oil which was dissolved in methanol, preadsorbed on silica and purified by flash column chromatography (ethyl acetate:cyclohexane, (1:1) → ethyl acetate) to afford 2-*C*-methyl-D-threono-1,4-lactone (R_f 0.56, 645 mg, 8%) as a yellow oil and

crude 2-*C*-methyl-D-erythrono-1,4-lactone (R_f 0.44, 660.4 mg). The crude 2-*C*-methyl-D-erythrono-1,4-lactone was dissolved in acetone (25 mL) and stirred at room temperature under an atmosphere of argon in the presence of *p*-toluenesulfonic acid monohydrate (477.4 mg, 2.51 mmol) for 16 hours, when TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.79). The reaction mixture was neutralised with excess sodium carbonate, filtered through a pad of Celite® with acetone and concentrated *in vacuo* to afford a crude yellow oil (572 mg). Purification by flash column chromatography (ethyl acetate:cyclohexane, (1:2) → ethyl acetate:cyclohexane, (1:1)) afforded 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone (243 mg, 2%) as a colourless oil. *Data for 2-*C*-methyl-D-threono-1,4-lactone*: ν_{max} (film): 3406 (br, O-H), 1775 (γ-lactone C=O) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.36 (3H, s, C$\underline{H}_3$), 3.98 (1H, dd, $J_{3,4}$ 4.4 Hz, $J_{4,4'}$ 9.4 Hz, H-4), 4.19 (1H, m, H-3), 4.50 (1H, dd, $J_{3,4'}$ 5.4 Hz, H-4') {Lit. δ_H (CD_3OD, 250 MHz): 1.30 (3H, s), 3.92 (1H, dd, ^2J 4.3 Hz, ^3J 9.2 Hz), 4.13 (1H, dd, ^2J 4.3 Hz, ^3J 5.5 Hz), 4.44 (1H, dd, ^2J 5.5 Hz, ^3J 9.2 Hz)}; δ_C (CD_3OD, 100.6 MHz): 16.59 ($\underline{C}H_3$), 71.84 (C-4), 74.53 (C-3), 74.87 (C-2), 179.03 (C-1) {Lit. δ_C (CD_3OD, 63 MHz): 17.9, 73.1, 78.8, 85.8, 161.8}; LRMS m/z (ESI -ve): 191.16 ($M+CH_3COO^-$, 60%), 263.24 ($2M-H^+$, 100%); HRMS m/z (FI +ve): found 132.0417 (M^+); $C_5H_8O_4$ requires 132.0423. *Data for 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone*: ν_{max} (film): 2939 & 2991 (C-H), 1785 (γ-lactone C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.38, 1.42 (2x3H, 2xs, C(C$\underline{H}_3$)$_2$), 1.53 (3H, s, C$\underline{H}_3$), 4.34 (1H, dd, $J_{4,4'}$ 11 Hz, $J_{3,4}$ 3.4 Hz, H-4), 4.39 (1H, d, H-4'), 4.48 (1H, d, H-3) {Lit. δ_H ($CDCl_3$, 360 MHz): 1.33 (3H, s), 1.37 (3H, s), 1.48 (3H, s), 4.24 (1H, dd, ^3J 3.54 Hz, ^2J 11.1 Hz), 4.34 (1H, dd, ^2J 11.1 Hz, ^3J 0 Hz), 4.41 (1H, dd, ^2J 3.5 Hz, ^3J 0 Hz)}; δ_C ($CDCl_3$, 100.6 MHz): 18.35 ($\underline{C}H_3$), 26.49, 26.90 (C($\underline{C}H_3$)$_2$), 68.90 (C-4), 80.30 (C-3), 81.38 (C-2), 112.92 ($\underline{C}(CH_3)_2$), 176.77 (C-1) {Lit. δ_C ($CDCl_3$, 90 MHz): 18.4, 26.5, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7}; HRMS m/z (FI +ve): found 172.0739 (M^+); $C_8H_{12}O_4$ requires 172.0736.

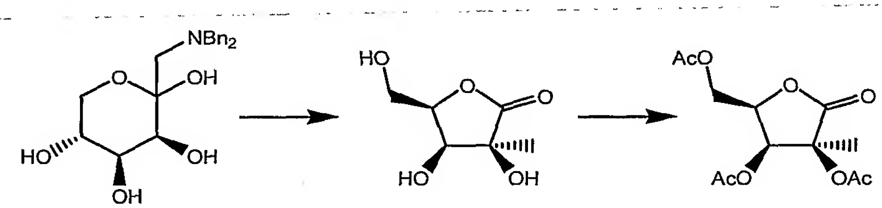
Example 8. **Synthesis of 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone from D-Galactose**



D-Galactose (10.44 g, 58.0 mmol) was suspended in ethanol (16.5 mL) with glacial acetic acid (3.3 mL). Dimethylamine solution (33% solution in methylated spirits, 10.6 mL, 59.6 mmol) was added to the suspension and the reaction mixture stirred at 80 °C for one and a half hours. The resulting dark orange solution was concentrated *in vacuo* to afford a crude dark orange-brown oil. The crude product mixture was then dissolved in water (300 mL) and stirred at 70 °C with calcium oxide (11.23 g, 200 mmol) for 24 hours. LRMS analysis (ESI -ve) of the crude alkaline reaction mixture showed only one major peak at 178.80 Da. Oxalic acid dihydrate (11.98 g, 95.0 mmol) was added to the suspension to afford a pale pink precipitate. The mixture was allowed to cool to room temperature, filtered through a pad of Celite® with water and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. The water was then removed under reduced pressure to afford a crude orange oil (8.64 g). The water was removed under reduced pressure, the crude product dissolved in methanol, preadsorbed on silica and eluted through a silica plug (ethyl acetate:cyclohexane, (1:1) → ethyl acetate) to afford a yellow solution with a measured pH of 0. The solvents were removed *in vacuo* and the crude product stirred under argon in acetone (50 mL). After 16 hours TLC analysis (ethyl acetate) revealed the presence of a product at R_f 0.75. The reaction mixture was neutralised with excess sodium carbonate, filtered through a pad of Celite® with acetone and concentrated *in vacuo* to afford a crude yellow oil. The crude product was dissolved in methanol, preadsorbed on silica and purified by flash column chromatography (ethyl acetate:cyclohexane, (1:2)) and subsequent recrystallisation from ethyl acetate by the addition of cyclohexane to afford 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone (205.3 mg, 2%) as a white crystalline solid; mp 155-158 °C {Lit. for 3,5-*O*-isopropylidene-2-*C*-methyl-L-xylono-1,4-lactone 155-157 °C};

$[\alpha]_D^{23}$ +82.2 (*c* 0.67 in $CHCl_3$) {Lit. for 3,5-*O*-isopropylidene-2-*C*-methyl-L-xylono-1,4-lactone $[\alpha]_D^{29}$ -73 (c 1.95 in $CHCl_3$)}; ν_{max} (film): 3422 (br, O-H), 1763 (γ-lactone C=O) {Lit. for 3,5-*O*-isopropylidene-2-*C*-methyl-L-xylono-1,4-lactone ν_{max}: 3420 (O-H), 1760 (γ-lactone C=O)} cm^{-1}; δ_H ($(CD_3)_2CO$, 400 MHz): 5.31 (1H, s, 2-OH), 4.54 (1H, ddd, $J_{4,5}$ 2.5 Hz, $J_{4,5'}$ 1.5 Hz, $J_{3,4}$ 2.5 Hz, H-4), 4.28 (1H, dd, $J_{5,5'}$ 14 Hz, H-5), 4.24 (1H, d, H-3), 4.04 (1H, dd, H-5'), 1.51, 1.36, 1.29 (9H, 3xs, 2-Me & CMe_2) {Lit. δ_H ($(CD_3)_2CO$): 5.22 (1H, br s, 2-OH), 4.55 (1H, q, $J_{3,4}$=$J_{4,5}$=$J_{4,5'}$ 2.25 Hz, H-4), 4.30 (1H, dd, $J_{5,5'}$ 13 Hz, H-5), 4.22 (1H, d, H-3), 4.01 (1H, dd, H-5'), 1.50, 1.35, 1.30 (9H, 3xs, 2-Me & CMe_2)}; δ_C ($(CD_3)_2CO$, 100.6 MHz): 16.72, 18.88, 28.65 (2-$\underline{C}H_3$ & $C(\underline{C}H_3)_2$), 59.92 (C-5), 71.51 (C-4), 73.60 (C-3), 76.71 (C-2), 97.70 ($\underline{C}(CH_3)_2$), 176.35 (C-1); LRMS m/z (ESI -ve): 201.07 ($M-H^+$, 60%). Found: C, 53.47; H, 7.00; $C_9H_{14}O_5$ requires C, 53.46; H, 6.98.

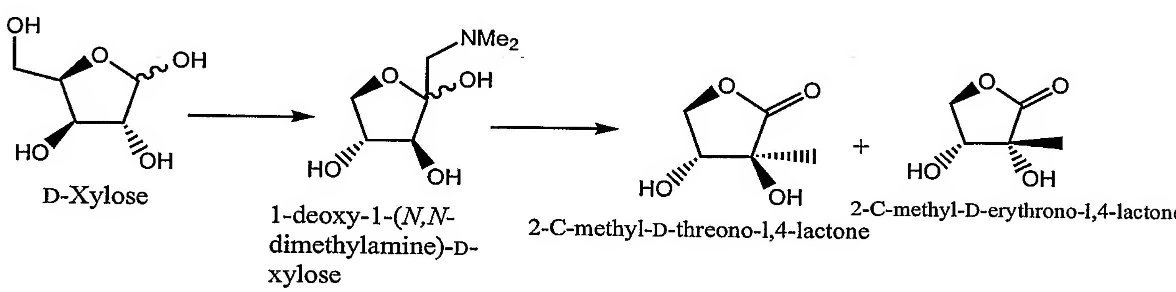
Example 9. Synthesis of 2-*C*-Methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone



1-Deoxy-1-(*N,N*-dibenzylamino)-D-tagatose (4.61 g, 12.84 mmol) was suspended in water (200 mL) and stirred at 70 °C with calcium hydroxide (7.44 g, 100.4 mmol) for 48 hours when TLC analysis (15% methanol in dichloromethane) revealed no starting material (R_f 0.63) and only baseline products which were not fluorescent under UV light. LRMS analysis (ESI -ve) of the crude alkaline reaction mixture showed only one major peak at 179.21 Da. Oxalic acid dihydrate (5.55 g, 44.0 mmol) was added to the suspension to afford a white precipitate suspended in a solution with a measured pH of 4. The mixture was allowed to cool to room temperature, filtered through Celite® and the filtrate passed through Amberlite® IR 120 ion exchange resin, using water as eluent. The water was then removed under reduced pressure to afford a crude orange oil (1.31 g). TLC analysis (15% methanol in dichloromethane) revealed the presence of one major product (R_f 0.38) which was purified by flash column chromatography (ethyl acetate) to afford a crude colourless oil. The crude oil was dissolved in dry pyridine (5 mL) and stirred with *N,N*-

dimethylaminopyridine (110 mg, 0.90 mmol) under an atmosphere of argon. Acetic anhydride (0.8 mL, 8.5 mmol) was added and the reaction mixture stirred for 16 hours when TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.79). Water (50 mL) was added to the reaction mixture and the solvents removed under reduced pressure to afford a crude brown oil. The crude product was purified by flash column chromatography (ethyl acetate:cyclohexane, 1:2) to afford 2-*C*-methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone (225 mg, 6%) as a colourless oil; $[\alpha]_D^{23}$ +75.8 (*c* 1.9 in $CHCl_3$); ν_{max} (film): 1749 (acetyl C=O), 1794 (γ-lactone C=O) cm^{-1}; δ_H (($CDCl_3$, 400 MHz): 1.69 (3H, s, C<u>H</u>$_3$), 2.06, 2.07 & 2.10 (9H, 3 x s, COC<u>H</u>$_3$), 4.26 (1H, dd, H-5), 4.34 (1H, dd, H-5'), 4.82 (1H, ddd, H-4), 5.71 (1H, d, $J_{3,4}$ 5.4 Hz, H-3); δ_C ($CDCl_3$, 100.6 MHz): 20.24 (<u>C</u>H$_3$), 20.48, 20.64, 20.66 (3 x CO<u>C</u>H$_3$), 61.28 (C-5), 72.03 (C-3), 76.41 (C-2), 76.16 (C-4), 168.72, 169.01, 170.37 (3 x <u>C</u>OCH$_3$), 171.96 (C-1); m/z (CI +ve): 289.08 (M+H$^+$, 76%), 306.12 (M+NH$_4$$^+$, 100%).

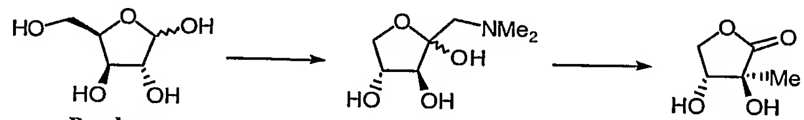
<u>Example 10.</u> Synthesis of 2-*C*-Methyl-D-threono-1,4-lactone and 2-*C*-Methyl-D-erythrono -1,4-lactone from D-Xylose



D-xylose (20.00 g, 130.04 mmol) was dissolved in water (100 mL) with acetic acid (7.6 mL). Dimethylamine (40% solution in water, 17.4 mL, 138.20 mmol) was added to the suspension and the reaction mixture was stirred al 80°C for 60 minutes. The resulting orange solution was cooled down to room temperature, and then calcium oxide (8.64 g, 154.00 mmol) was added and the mixture was stirred at 70°C for 16 hours. The mixture was allowed to cool at room temperature, filtered through celite and the filtrate was passed through a column of Amberlite IR-120. TLC analysis (ethyl acetate) showed a major product (Rf 0.48) and a minor one (Rf 0.35). The solvent was evaporated to obtain an oil, which was preadsorbed on silica and purified by flash column chromatography (ethyl acetate/cyclohexane 4:1→8:1) to afford 2-*C*-

methyl-D-*threono*-1,4-lactone (1.86 g, 10.6%) as an orange oil and 2-*C*-methyl-D-*erythrono*-1,4-lactone (0.68 g, 3.9%) as a dark yellow oil.

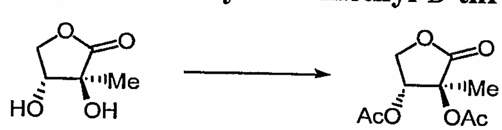
Example 11. Alternative Synthesis of 2-*C*-Methyl-D-threono-1,4-lactone from D-Xylose



D-xylose 600 601

D-Xylose (10.00 g, 65.02 mmol) was suspended in ethanol (15 mL) with acetic acid. Dimethylamine (33% solution in methylated spirit, 12 mL, 69.1 mmol) was added to the suspension and the reaction mixture was stirred al 80 °C for 30 min. The resulting orange solution was evaporated *in vacuo* to give a crude oil, which was used without any further purification. This crude product was dissolved in water (300 mL) and stirred with calcium oxide (12.95 g, 231 mmol) at 70 °C for 16 h. The mixture was allowed to cool at room temperature, filtered through Celite® and the filtrate was passed through a column of Amberlite® IR-120. TLC analysis (ethyl acetate) showed a single product (Rf 0.48). The solvent was evaporated to obtain an oil, which was preadsorbed on silica and purified by flash column chromatography (ethyl acetate/cyclohexane 4:1) to afford 2-*C*-methyl-D-threono-1,4-lactone (0.95, 11%) as a dark yellow oil; ν_{max} (NaCl): 3406 (-OH); 1775 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.36 (s, 3H, -CH_3), 3.98 (dd, 1H, $J_{3,4}$ 4.4 Hz, $J_{4,4'}$ 9.4 Hz, H_4), 4.19 (m, 1H, H_3), 4.50 (dd, 1H, $J_{3,4'}$ 5.4 Hz, $J_{4,4'}$ 9.4 Hz, $H_{4'}$); δ_C (Cl_3CD): 16.59 (-CH_3), 71.84 (C_4), 74.53 (C_3), 74.87 (C_2), 179.03 (C_1); *m/z* (NH_3, ES-): 131 $(M-H)^-$.

Example 12. Synthesis of 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone

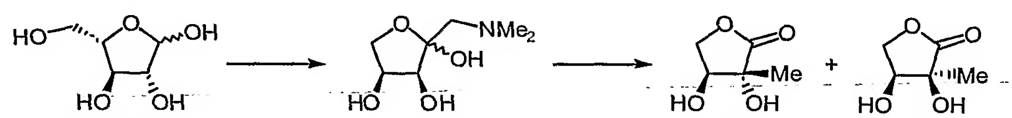


601 602

To a solution of 2-*C*-methyl-D-threono-1,4-lactone (68.8 mg, 0.52 mmol) in pyridine (2 mL), DMAP (13.1 mg, 0.10 mmol) and acetic anhydride (0.2 mL, 2.08 mmol) were added and the reaction mixture was stirred at room temperature for 3 h.

TLC (ethyl acetate/cyclohexane) revealed absence of starting material and a single product. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane 1:2) to yield 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone (83.1 mg, 74%); $[\alpha]_D^{22}$ -50.3 (*c*, 1.5 in chloroform); ν_{max} (NaCl): 1739, 1791 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.45 (s, 3H, -CH_3), 2.08, 2.09 (2 x s, 6H, 2 x -COCH_3), 3.98 (dd, 1H, $J_{3,4}$ 6.4 Hz, $J_{4,4'}$ 10.0 Hz, H_4), 4.74 (dd, 1H, $J_{3,4'}$ 8.0 Hz, $J_{4,4'}$ 10.0 Hz, $H_{4'}$), 5.68 (dd, 1H, $J_{3,4}$ 6.4 Hz, $J_{3,4'}$ 8.0 Hz, H_3); δ_C (Cl_3CD): 17.34 (-CH_3), 20.32, 20.35 (2 x -COCH_3), 68.45 (C_4), 72.39 (C_3), 77.89 (C_2), 112.92 (-*C*(CH_3)$_2$), 169.74, 170.22 (2 x -*C*OCH_3), 172.34 (C_1); *m/z* (NH_3, ES+): 217 $(M+H)^+$; HRMS: found 217.0712 $(M+H)^+$; $C_9H_{13}O_6$ requires 217.0709.

Example 13. Synthesis of 2-*C*-methyl-L-threono-1,4-lactone and 2-*C*-methyl-L-erythrono-1,4-lactone



L-arabinose 605 610 611

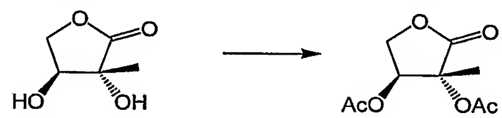
L-Arabinose (10.00 g, 65.02 mmol) was suspended in ethanol (15 mL) with acetic acid. Dimethylamine (33% solution in methylated spirit, 12 mL, 69.1 mmol) was added to the suspension and the reaction mixture was stirred al 80 °C for 30 min. The resulting orange solution was evaporated *in vacuo* to give a crude oil, which was used without any further purification. This crude product was dissolved in water (300 mL) and stirred with calcium oxide (12.95 g, 231 mmol) at 70 °C for 16 h. The mixture was allowed to cool at room temperature, filtered through Celite® and the filtrate was passed through a column of Amberlite® IR-120. TLC analysis (ethyl acetate) showed a major product (Rf 0.48) and a minor one (Rf 0.35). The solvent evaporated to obtain an oil, which was preadsorbed on silica and purified by flash column chromatography (ethyl acetate/cyclohexane 4:1→8:1) to afford 2-*C*-methyl-L-threono-1,4-lactone (0.68, 8%) as a dark yellow oil and 2-*C*-methyl-L-erythrono-1,4-lactone (0.36, 4%) as a yellow oil.

Data for 2-*C*-methyl-L-threono-1,4-lactone: ν_{max} (NaCl): 3406 (-OH); 1775 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.36 (s, 3H, -CH_3), 3.98 (dd, 1H, $J_{3,4}$ 4.4 Hz, $J_{4,4'}$ 9.4 Hz, H_4), 4.19

(m, 1H, H_3), 4.50 (dd, 1H, $J_{3,4'}$ 5.4 Hz, $J_{4,4'}$ 9.4 Hz, $H_{4'}$); δ_C (Cl_3CD): 16.59 (-CH_3), 71.84 (C_4), 74.53 (C_3), 74.87 (C_2), 179.03 (C_1); *m/z* (NH_3, ES-): 131 $(M-H)^-$.

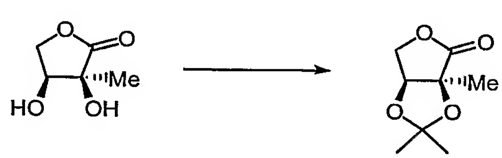
Data for 2-*C*-methyl-L-erythrono-1,4-lactone: ν_{max} (NaCl): 3398 (-OH); 1774 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.47 (s, 3H, -CH_3), 4.15-4.16 (m, 1H, H_4), 4.35 (d, 1H, $J_{3,4}$ 1.0 Hz, H_3), 4.37-4.38 (m, 1H, $H_{4'}$); δ_C (Cl_3CD): 20.98 (-CH_3), 66.45 (C_4), 73.18 (C_3), 73.72 (C_2), 178.95 (C_1); *m/z* (NH_3, ES-): 131 $(M-H)^-$.

Example 14. Synthesis of 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone



To a solution of 2-*C*-methyl-L-threono-1,4-lactone (80.0 mg, 0.47 mmol) in pyridine (2 mL), DMAP (13.1 mg, 0.10 mmol) and acetic anhydride (0.2 mL, 1.88 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. TLC analysis (ethyl acetate/cyclohexane) revealed absence of starting material and a single product. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane 1:2) to yield 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone (63.5 mg, 63%), $[\alpha]_D^{22}$ +47.9 (*c*, 1.3 in chloroform); ν_{max} (NaCl): 1739, 1791 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.45 (s, 3H, -CH_3), 2.08, 2.09 (2 x s, 6H, 2 x -$COCH_3$), 3.98 (dd, 1H, $J_{3,4}$ 6.4 Hz, $J_{4,4'}$ 10.0 Hz, H_4), 4.74 (dd, 1H, $J_{3,4'}$ 8.0 Hz, $J_{4,4'}$ 10.0 Hz, $H_{4'}$), 5.68 (dd, 1H, $J_{3,4}$ 6.4 Hz, $J_{3,4'}$ 8.0 Hz, H_3); δ_C (Cl_3CD): 17.34 (-CH_3), 20.32, 20.35 (2 x -$COCH_3$), 68.45 (C_4), 72.39 (C_3), 77.89 (C_2), 112.92 (-$C(CH_3)_2$), 169.74, 170.22 (2 x -$COCH_3$), 172.34 (C_1); *m/z* (NH_3, ES+): 217 $(M+H)^+$; $C_9H_{13}O_6$ requires C 50.00, H 5.59 found C 50.26, H 5.69.

Example 15. Synthesis of 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone



611 613

To a solution of 2-*C*-methyl-L-erythrono-1,4-lactone (0.11 g, 0.85 mmol) in acetone (4 mL), *p*-toluenesulfonic acid (0.03 g, 0.17 mmol) was added and the

mixture was stirred at room temperature for 14 h. TLC (ethyl acetate) revealed absence of starting material and a single product (Rf 0.70). The mixture was then neutralized with solid sodium carbonate, filtered and the solvent evaporated. The residue was shaken with DCM (10 mL) and water (10 mL) and the aqueous layer was further extracted with DCM (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to produce a residue which was purified by flash chromatography (ethyl acetate/cyclohexane 1:2) to afford 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone (0.49 g, 40%), $[\alpha]_D^{22}$ +85.3 (*c*, 1.5 in chloroform); ν_{max} (NaCl): 1785 (-C=O) cm^{-1}; δ_H (Cl_3CD): 1.41, 1.45 (2 x s, 6H, -C(CH_3)$_2$), 1.55 (s, 3H, -CH_3) 4.31 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,4'}$ 11.0 Hz, H_4), 4.39 (d, 1H, $J_{4,4'}$ 11.0 Hz, $H_{4'}$), 4.48 (d, 1H, $J_{3,4}$ 3.4 Hz, H_3); δ_C (Cl_3CD): 18.35 (-CH_3), 26.49, 26.90 (-C(CH_3)$_2$), 68.90 (C_4), 80.30 (C_3), 81.38 (C_2), 112.92 (-*C*(CH_3)$_2$), 176.77 (C_1); *m/z* (NH_3, ES+): 190 $(M+NH_4)^+$; HRMS: found 172.0739 (M^+); $C_8H_{12}O_4$ requires 172.0736.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed processes and reaction conditions. Variations that are obvious to one of ordinary skill in the art are intended to be included within the spirit and scope of the invention as defined in the appended claims.

Claims

We claim:

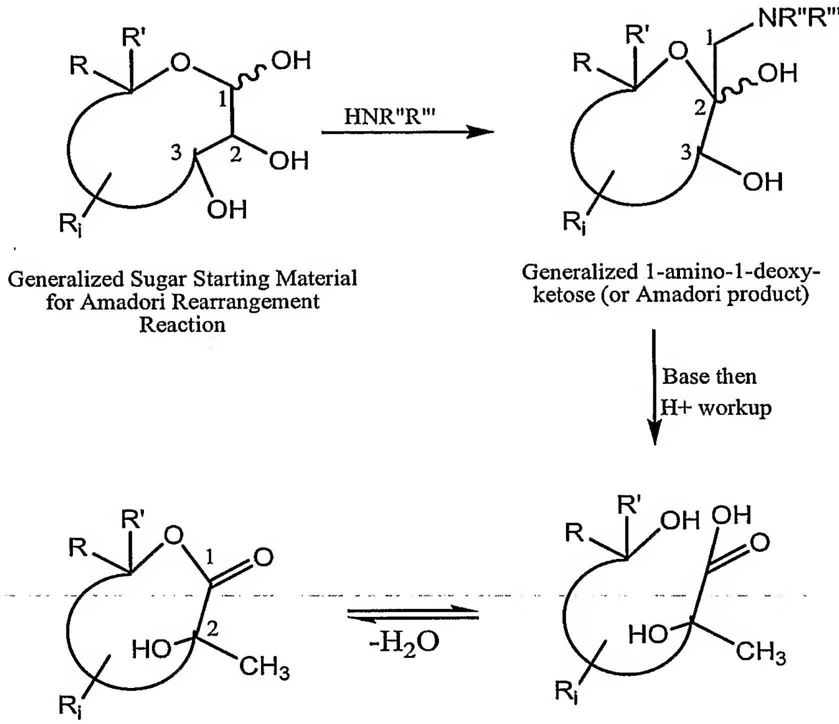
1. A process for preparing a saccharinic acid or lactone in all its stereochemical and tautomeric forms comprising:
   a. reacting a sugar with a disubstituted amine to provide, via an Amadori rearrangement reaction, a corresponding disubstituted amino sugar;
   b. reacting the disubstituted amino sugar with a base and optionally subsequently with an acid to afford a saccharinic acid or lactone product.
2. The process of claim 1 further comprising protecting the saccharinic acid or lactone product with a protecting group.
3. The process of claim 1 wherein the saccharinic acid or lactone product is purified.
4. The process of claim 1 wherein no intermediate product isolation occurs between steps (a) and (b).
5. The process of claim 1 wherein the sugar is selected from the group consisting of glucose, fructose, arabinose, galactose, xylose, and tagatose.
6. The process of claim 1 wherein the sugar is in D- or L- stereoisomeric form.
7. The process of claim 1 wherein the disubstituted amine is dimethylamine or dibenzylamine.
8. The process of claim 1 wherein the base is calcium hydroxide or calcium oxide.
9. The process of claim 6 wherein the base is calcium oxide.
10. The process of claim 1 wherein the acid is sulfuric acid.
11. The process of claim 1 wherein step (a) is carried out at from about 40°C to about 120°C.
12. The process of claim 9 wherein step (a) is carried out at from about 70°C to about 90°C.
13. The process of claim 1 wherein step (b) is carried out at from about 20°C to about 120°C.
14. The process of claim 11 wherein step (b) is carried out at from about 60°C to about 80°C.

15. The process of claim 1 wherein the total reaction time is from about 15 hours to about 96 hours.
16. The process of claim 9 wherein the reaction time is from about 10 minutes to about 10 hours.
17. The process of claim 14 wherein the reaction time is from about 30 minutes to about 5 hours.
18. The process of claim 11 wherein the reaction time is from about 12 hours to about 96 hours.
19. The process of claim 16 wherein the reaction time is from about 15 hours to about 50 hours.
20. The process of claim 1, wherein in step (c) the reaction time is from about 2 hours to about 15 hours.
21. The process of claim 1 wherein the saccharinic acid or lactone product is isolated by filtration and passage through an ion exchange resin.
22. The process of claim 1 wherein the saccharinic acid or lactone product is purified by chromatography.
23. The process of claim 1 wherein the saccharinic acid or lactone product is isolated by filtration, evaporation, extraction and crystallization.
24. The process of claim 1, wherein, the lactone is 2-*C*-methyl-D-ribono-1,4-lactone; the sugar compound is D-glucose ; the disubstituted amine is dimethylamine; and the acid is sulfuric acid.
25. The process of claim 1, wherein, the lactone is 2-*C*-methyl-D-ribono-1,4-lactone; the sugar is D-glucose; the disubstituted amine is dimethylamine or dibenzylamine; the acid is oxalic acid; and the lactone is purified by chromatography.
26. The process of claim 1, wherein, the lactone is a mixture of 2-*C*-methyl-D-lyxono-1,4-lactone and 2-*C* methyl-D-xylono-1,4-lactone; the sugar is D-galactose ; the disubstituted amine is dibenzylamine; and the base is calcium oxide.
27. Any one of the processes of claims 1, 22, 23, or 24 wherein the purification is by flash chromatography.
28. The process of claim 1 wherein the sugar compound is D-xylose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-D-threono-1,4-lactone and 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone.

29. The process of claim 1 wherein the sugar compound is D-xylose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-D-threono-1,4-lactone and 2-*C*-methyl-D-erythrono-1,4-lactone.
30. The process of claim 1 wherein the sugar compound is D-galactose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone product is 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone.
31. The process of claim 1 wherein the sugar compound is D-galactose, the disubstituted amine is dibenzylamine, the base is calcium hydroxide, and the saccharinic lactone product is 2-*C*-methyl-2,3,5-tri-*O*-acetyl-D-lyxono-1,4-lactone.
32. The process of claim 1 wherein the sugar compound is L-arabinose, the disubstituted amine is dimethylamine, the base is calcium oxide, and the saccharinic lactone products are 2-*C*-methyl-L-threono-1,4-lactone and 2-*C*-methyl-L-erythrono-1,4-lactone.
33. A process for preparing an hydroxy-protected saccharinic lactone comprising:
    a. reacting a saccharinic lactone with pyridine to afford a saccharinic lactone solution;
    b. reacting the saccharinic lactone solution with an hydroxy-protective reagent to form an hydroxy-protected saccharinic lactone; and
    c. isolating and/or purifying the hydroxy-protected saccharinic lactone product.
34. The process of claim 31 wherein the hydroxyl-protective reagent is acetic anhydride.
35. The process of claim 31 wherein the saccharinic lactone is 2-*C*-methyl-D-threono-1,4-lactone and the hydroxy-protected saccharinic lactone is 2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone.
36. The process of claim 31 wherein the saccharinic lactone is 2-*C*-methyl-L-threono-1,4-lactone and the hydroxy-protected saccharinic lactone is 2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone.
37. The process of claim 31 wherein the saccharinic lactone is 2-*C*-methyl-D-lyxono-1,4-lactone and the hydroxyl-protected saccharinic lactone is 2,3,5-tri-*O*-acetyl-2-*C*-methyl-D-lyxono-1,4-lactone.

38. A process for preparing an hydroxy-protected saccharinic lactone comprising:
    a. reacting a saccharinic lactone with an acidic solution to afford a saccharinic lactone solution;
    b. reacting the saccharinic lactone acidic solution with an hydroxyl-protecting reagent to provide an hydroxyl-protected saccharinic lactone; and
    c. isolating and/or purifying the hydroxy-protected saccharinic lactone.
39. The process of claim 36 wherein the acidic solution comprises acetone in a dilute *p*-toluenesulfuric acid solution.
40. The process of claim 36 wherein the saccharinic lactone is 2-*C*-methyl-D-xylono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone.
41. The process of claim 36 wherein the saccharinic lactone is 2-*C*-methyl-D-erythrono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone.
42. The process of claim 36 wherein the saccharinic lactone is 2-*C*-methyl-L-erythrono-1,4-lactone and the hydroxyl-protected saccharinic lactone product is 2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone.

Figure 1



R, R', R", R''' and R_i are various substituents of choice; ring size is as desired.

Figure 2

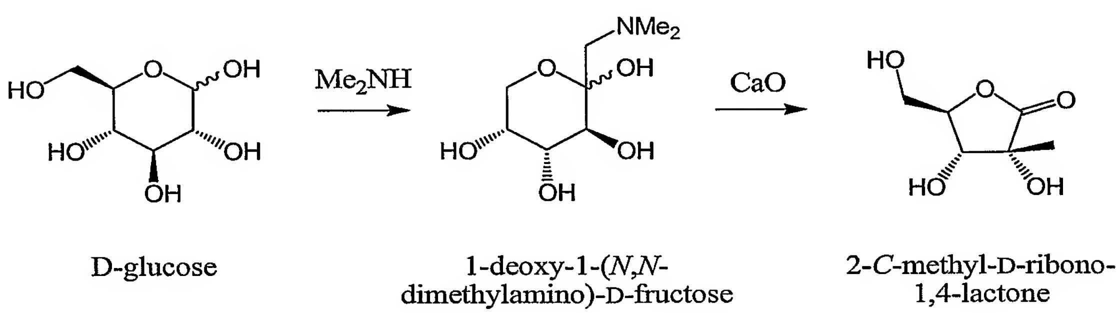
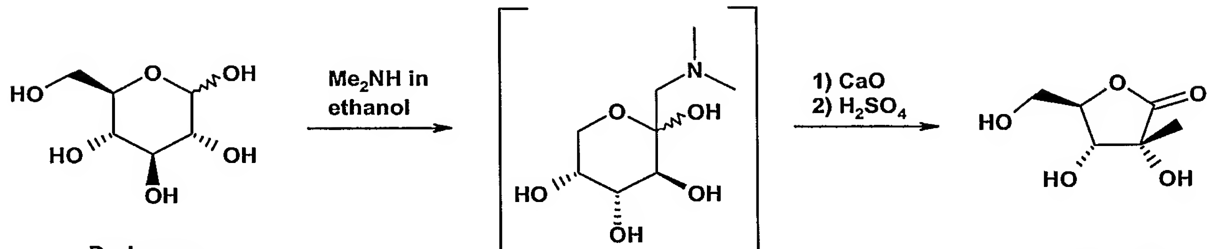


Figure 2a



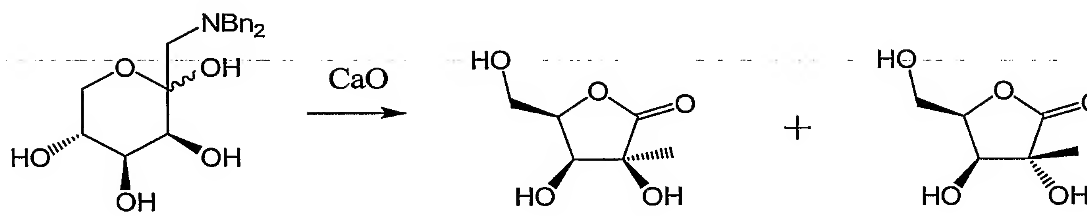
D-glucose

1-deoxy-1-(*N,N*-dimethylamino-D-fructose

Compound 2

2-C-methyl-D-ribono-1,4-lactone

Figure 3

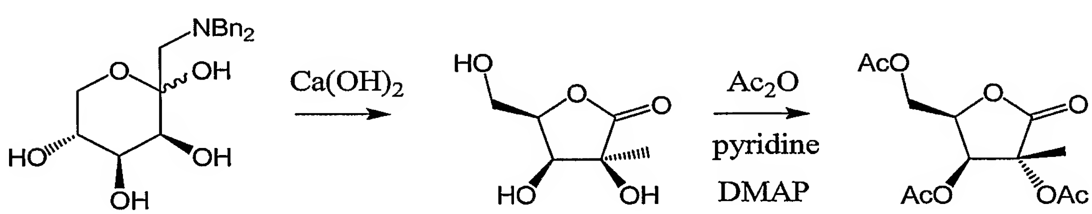


1-deoxy-1-(*N,N*-dibenzylamino)-D-tagatose

2-*C*-methyl-D-lyxono-1,4-lactone

2-*C*-methyl-D-xylono-1,4-lactone

Figure 4

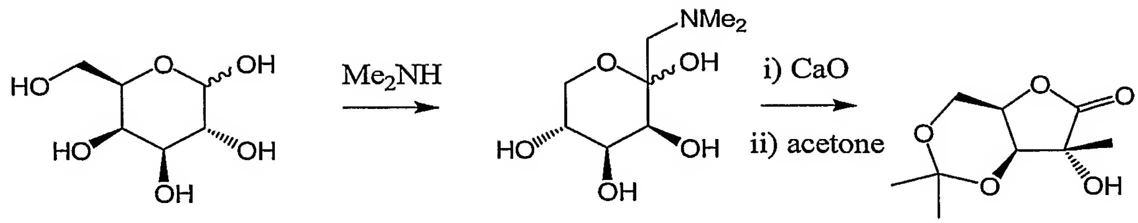


1-deoxy-1-(*N,N*-dibenzylamino)-D-tagatose

2-*C*-methyl-D-lyxono-1,4-lactone

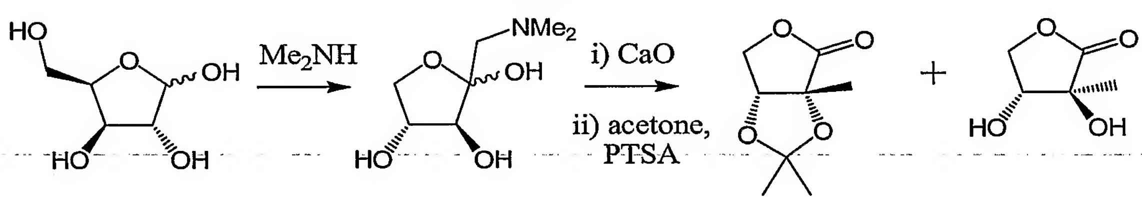
2,3,5-tri-*O*-acetyl-2-*C*-methyl-D-lyxono-1,4-lactone

Figure 5



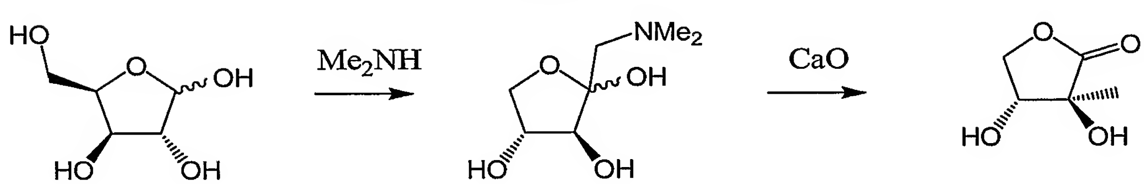
D-galactose | 1-deoxy-1-(*N*,*N*-dimethylamino)-D-tagatose | 3,5-*O*-isopropylidene-2-*C*-methyl-D-xylono-1,4-lactone

Figure 6



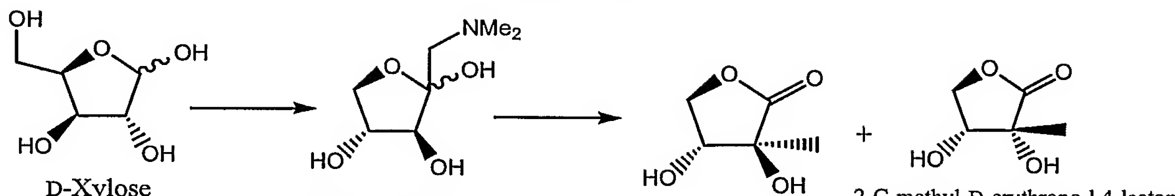
D-xylose | 1-deoxy-1-(*N*,*N*-dimethylamino)-D-xylulose | 2,3-*O*-isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone | 2-*C*-methyl-D-threono-1,4-lactone

Figure 7



D-xylose | 1-deoxy-1-(*N*,*N*-dimethylamino)-D-xylulose | 2-*C*-methyl-D-threono-1,4-lactone

Figure 7a



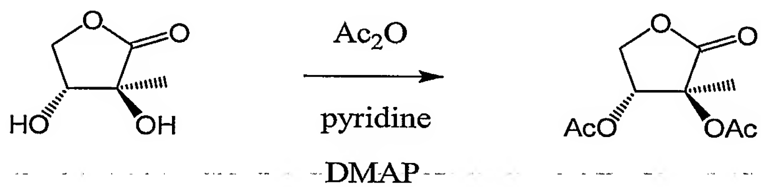
D-Xylose

1-deoxy-1-(*N,N*-dimethylamine)-D-xylose

2-C-methyl-D-threono-1,4-lactone

2-C-methyl-D-erythrono-1,4-lactone

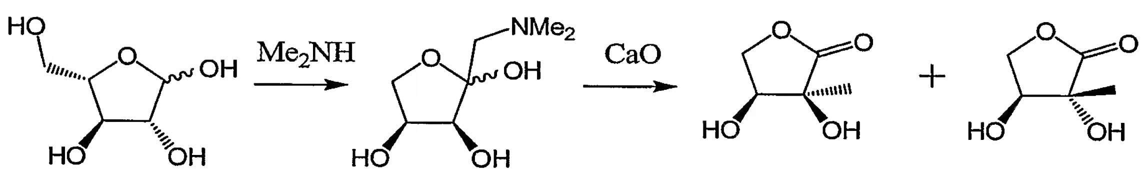
Figure 8



2-*C*-methyl-D-threono-1,4-lactone

2,3-di-*O*-acetyl-2-*C*-methyl-D-threono-1,4-lactone

Figure 9



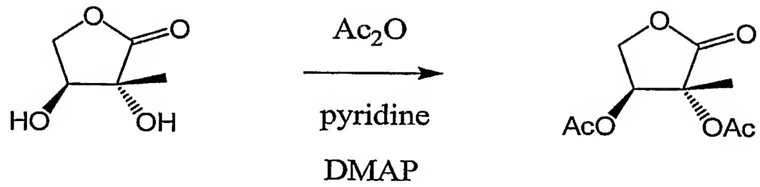
L-arabinose

1-deoxy-1-(*N,N*-dimethylamino)-L-arabinulose

2-*C*-methyl-L-erythrono-1,4-lactone

2-*C*-methyl-L-threono-1,4-lactone

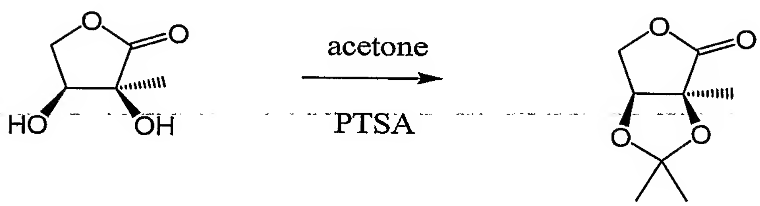
Figure 10



2-*C*-methyl-L-threono-1,4-lactone

2,3-di-*O*-acetyl-2-*C*-methyl-L-threono-1,4-lactone

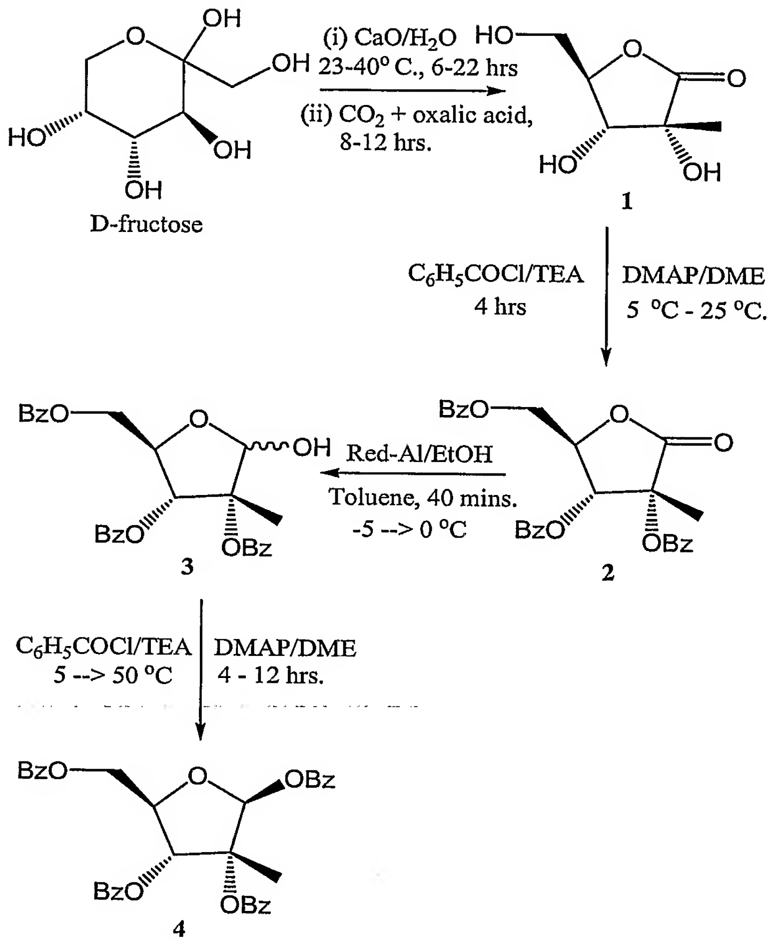
Figure 11



2-*C*-methyl-L-erythrono-1,4-lactone

2,3-*O*-isopropylidene-2-*C*-methyl-L-erythrono-1,4-lactone

Figure 12


OH
OH
HO
OH
OH
D-fructose
(i) CaO/H2O
23-40° C., 6-22 hrs
(ii) CO2 + oxalic acid,
8-12 hrs.
HO
O
O
HO
OH
1
C6H5COCl/TEA
4 hrs
DMAP/DME
5 °C - 25 °C.
BzO
O
O
BzO
OBz
2
Red-Al/EtOH
Toluene, 40 mins.
-5 --> 0 °C
BzO
O
OH
BzO
OBz
3
C6H5COCl/TEA
5 --> 50 °C
DMAP/DME
4 - 12 hrs.
BzO
O
OBz
BzO
OBz
4